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A STUDY OF DETERMINANTS OF MALARIA IN KELANTAN, MALAYSIA

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI‘I IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN BIOMEDICAL SCIENCES (BIOSTATISTICS-EPIDEMILOGY)

AUGUST 1995

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ABSTRACT

The candidate conducted operational research, in collaboration with the Vector-Borne Diseases Control Program (VBDCP), Kelantan, Malaysia, to analyze determinants of malaria incidence at different geographic scales: the state (inter-annual and intra-annual rainfall, and other seasonal events); the district (age- and sex-specific risk groups in relation to blood-film collection methods: Passive Case Detection [PCD], Active Case Detection [ACD], Investigation Surveys [INV]); and the village/individual domicile (environmental and behavioral variables). Routine operational data from the VBDCP were used as far as possible.

Statewide statistics showed clear association of malaria with intra-annual rainfall variation but in a mixed correlation: high or low rainfall reduce malaria incidence, while moderate rainfall increases incidence. Inter-annual El Niño Southern Oscillation events, which cause drought in southeast Asia, were associated with reduced malaria incidence. Rubber price and production, and fruit seasons could not be conclusively associated with incidence.

All malaria blood-films examined during 1991 in Gua Musang district were entered to a database permitting age- and sex-stratified analysis of the populations sampled by PCD, ACD, and INV. Relative to the census population, the blood-film collection over-samples children and young adult males, but these risk groups still have higher incidence. PCD was most efficient in detecting malaria cases, but ACD and INV were most effective in detecting falciparum gametocytemia.

A case-control study of behavioral and environmental determinants of malaria (largely taken from the routine case investigation form) in Jerek village proved inconclusive due to small sample size, resulting from low malaria transmission.
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<td>ABER</td>
<td>Annual Blood Examination Rate [total blood-films/total population]</td>
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<tr>
<td>ACD</td>
<td>Active Case Detection</td>
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<td>API</td>
<td>Annual Parasite Incidence [total positive blood-films/total population]</td>
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<tr>
<td>Bti</td>
<td><em>Bacillus thuringiensis israeliensis</em></td>
</tr>
<tr>
<td>ENSO</td>
<td>El Niño Southern Oscillation</td>
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<td>INV</td>
<td>Investigation Survey</td>
</tr>
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<td>MBS</td>
<td>Mass Blood Survey</td>
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<td>MCP</td>
<td>Malaria Control Program</td>
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<td>MDA</td>
<td>Mass Drug Administration</td>
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<td>MEP</td>
<td>Malaria Eradication Program</td>
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<tr>
<td>PCD</td>
<td>Passive Case Detection</td>
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<td>Pf</td>
<td><em>Plasmodium falciparum</em></td>
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<td>Pv</td>
<td><em>Plasmodium vivax</em></td>
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<td>RKPBV</td>
<td>Rancangan Kawalan Penyakit-Penyakit Bawaan Vektor [Vector-Borne Diseases Control Program]</td>
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<td>SPR</td>
<td>Slide Positivity Rate [total positive blood-films/total blood-films]</td>
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<td>Vector-Borne Diseases Control Program</td>
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CHAPTER 1: INTRODUCTION

Malaria is the most important public health problem in the world, when annual morbidity and mortality are considered (270 million cases/year and 1-2 million deaths/year; World Health Organization, 1991; UNDP/World Bank/WHO, 1991). Although important reduction, even eradication, of malaria was achieved in temperate regions of the world and some tropical areas (mainly islands), transmission continues in virtually all tropical regions, with 2.1 billion people at risk. Prospects for major reduction of malaria incidence are not promising, even if a practical vaccine emerges from current research (UNDP/World Bank/WHO, 1994). Longstanding obstacles to effective malaria control are not improving, such as lack of sterile immunity in recovered patients, difficulty in delivery of medical services, reduction of health budgets and donor support, population mobility, drug-resistance in the parasite, and insecticide-resistance or behavioral intractability in vector mosquitoes.

Malaria transmission, a complex multifactorial process, has proven resilient to broad interventions, such as residual intradomiciliary insecticiding and mass drug administration. When the failure of the global eradication campaign was conceded in the 1970s, the WHO Seventeenth Expert Committee on Malaria (World Health Organization, 1979) endorsed an "epidemiological approach" to the control of malaria through the application of control tactics adapted to local needs and resources, but the epidemiological approach has proven difficult to implement. Most malaria eradication programs became malaria control programs keeping the same strategy and tactics.
The status of information and the scope of research on malaria are paradoxical. From 1900 to 1950 (pre-DDT eradication era), a great deal of work contributed to basic knowledge of the parasite lifecycle, vector bionomics, and environmental sanitation measures; ironically, the malaria eradication era, by its focus on a single tactic (residual DDT house-spraying), tended to eradicate the multifactorial approach to understanding of and intervention against malaria (Harrison, 1978).

In the post-eradication era, new work has resulted in much knowledge about the parasites, the vector mosquitoes, and the host, in terms of molecular biology and genetics, immunology, and biochemistry. Yet, little seems to change in our ability to effectively intervene against malaria.

In this dissertation, the candidate carried out a case-referent study in a malarious village using the standard behavioral and environmental determinants (risk-factors) of malaria that appear on the case investigation form; also carried out a census study of all blood-filmed individuals in Gua Musang district during one year, to identify age-sex strata with higher risk of malaria (asexual and gametocyte infection) in relation to three detection methods; finally, gathered data on rainfall to assess the relationship of this large-scale determinant on intra- and inter-annual variation of malaria incidence.

MALAYSIA

Malaria in Malaysia (1991 population = 17,566,982; Department of Statistics, 1993) is still a major public health problem, even though incidence has decreased over the decades (Kondrashin, 1986; Ayyamni and Chee, 1988). From 1960 to 1979, during the malaria eradication program (MEP), malaria incidence steadily dropped from an estimated 250,000 cases/year to 50,000/year (Mak et al., 1992). Since 1980,
crude annual parasite incidence (API) has varied as high as 4.3/1000 and as low as 1.5/1000 (Figure 1). In 1992, the crude API was 2.0/1000 (VBDCP Malaysia, 1993), but this underestimates the true risk in malaria transmission areas, since there is no transmission in urban areas (Malaria-Free areas where 67% of the population live). The API in malaria-problem areas was 16.4/1000 (VBDCP Malaysia, 1993).

It is important to note that large differences exist between the three geographic regions of Malaysia, 1) Peninsular Malaysia (comprised of 11 states that became independent in 1957), 2) Sarawak, and 3) Sabah (the latter two territories, on the island of Borneo, joined the Federation in 1962).

**Peninsular Malaysia**

In Peninsular Malaysia, malaria has receded from the coastal and heavily populated areas, partly due to success of the malaria control strategy, and partly to general improvements in socioeconomic development (Malaria-Free zones). The interior, rural, forest, and mountain areas remain Malaria-Problem zones. In between are developing areas defined as Malaria-Prone, where transmission has declined, but surveillance for new cases continues. Of the 11 states in Peninsular Malaysia (Figure 2), malaria transmission is high in four: Kelantan, Pahang, Perak, and Johore (VBDCP Malaysia, 1993).

The important mosquito vectors in Peninsular Malaysia breed in rural areas. As the population increasingly lives in urban or periurban areas, the result is lower risk of contact with infective mosquitoes, as well as rising standards of housing, preventative measures, and delivery of health and medical care. Countervailing these trends have
been large land development schemes for agriculture which bring both temporary
tropical labor aggregation and permanent settlement into Malaria-Problem zones.

*Anopheles maculatus* is the principal vector of malaria in Peninsular Malaysia
breeding in sunlit seepages or slow-moving streams, in hilly country, villages,
plantations, and forest. In some densely populated areas, anti-larval drainage was
successfully applied to control *An. maculatus* (Moorhouse, 1965) but not in sparsely
settled rural areas. Furthermore, residual house spraying was never wholly successful
in controlling malaria, even in the original trial projects during the 1950s (Edeson
*et al.*, 1957). This was due to the exophilic, exophagic behavior of the vector, and the
excito-repellent effect of DDT (Wallace, 1950). Selection for DDT-resistance has not
occurred during 30 years of spraying, indicating that the DDT interferes with human-
vector contact as a repellent rather than killing *An. maculatus* (Loong *et al.*, 1989).

*An. campestris* is a secondary vector breeding in rice-growing and coastal areas.
It was observed during the 1960s that *An. campestris* was exquisitely sensitive to
residual house spraying: two cycles of DDT spraying completely interrupted malaria
transmission (Huehne, 1971a, 1971b). *An. sundaicus* is considered a marginal vector
in coastal areas, breeding in brackish water, causing epidemic outbreaks under
conditions of unusually high vector density. *An. letifer* has been incriminated as a
vector in coastal plains. Finally, *An. balabacensis/An. dirus* is found in low density in
the northern states, but unlike Thailand to the north, this species complex is not
considered an important vector in Peninsular Malaysia.

**Sabah**

In Sabah (one of the two Malaysian states on Borneo), malaria incidence is the
highest in Malaysia, since the 1970s, and difficult to control, due to the vector *An.*
balabacensis s.s., a notorious and efficient vector in southeast Asia (An. balabacensis/An. dirus species complex); a largely rural, agricultural population, living in rough or insubstantial housing; land development projects; and logistical difficulty in applying malaria control strategy.

An. balabacensis breeds in very small, rain-freshened collections of water in the forest or plantation. Natural puddles, water buffalo hoofprints, human footprints, vehicle tracks are all possible breeding sites. Some limited anti-larval drainage is feasible, e.g., in plantations, but otherwise, larval control is impossible. Residual house spraying is compromised by the flimsy or incomplete walls of most rural housing, or the excito-repellent effect of DDT (Cheng, 1968) that keeps the adult vector outside of sprayed houses with substantial walls. As with An. maculatus in Peninsular Malaysia, malaria transmission has been reduced but not interrupted, while selection for insecticide-resistance in An. balabacensis has not occurred after 30-40 years of spraying.

An. sundaicus and An. letifer are two closely related species, brackish water breeders, that are associated with irregular epidemic outbreaks, but not regular transmission. An. flavirostris is the most recently incriminated vector (Hii et al., 1985b).

Sarawak

In Sarawak (one of the two Malaysian states on Borneo), malaria incidence has been very low (less than 1000 cases/year) since a successful malaria control strategy during 1953-70s, apparently due to a different vector (An. leucosphyrus) together with extremely effective malaria intervention and different sociodemographics. Although
roads were few and rudimentary during the period, most of the interior (ulu) population lived in contained longhouses situated along navigable rivers. Personal protection measures may have been important; bednet usage is a standard and widespread practice (personal observation). Logging and land development came later to Sarawak than Sabah, so this transmission stimulus was absent during the MEP.

*An. leucosphyrus* is the primary vector in Sarawak, while *An. sundaicus* is a secondary vector. However, the small amount of malaria transmission in Sarawak is recorded largely in the border areas with Sabah where *An. balabacensis* is found.

**EPIDEMIOLOGICAL CONDITIONS**

A great deal is known about the epidemiology of malaria in Malaysia, while at the same time we know very little about the risk factors (determinants) associated with variation in malaria transmission within Malaysia. A recent review article (Mak et al., 1992) states,

"Intense longitudinal studies have therefore been conducted during the last couple of years to define the epidemiological conditions contributing to this situation [high malaria morbidity in spite of thirty years' existence of a malaria control program]..."

but without citing any such studies. The epidemiological conditions contributing to continued transmission are general and qualitative:

- development of drug resistant *Plasmodium falciparum*,
- changes in vector behavior,
- ecological changes due to socio-economic changes,
- malaria parasite rates are higher among the Aborigines, land scheme settlers, and those in intimate contact with the jungle. (Mak et al., 1992)
Ayyamni and Chee (1988) reported a slightly different group of factors:

- the clearing up of vast tracts of jungle for land development schemes,
- road and dam constructions,
- nomadic Orang Asli (aborigines) population in inaccessible hinterland areas,
- movements of security forces in and out of jungle areas,
- movements of people across international borders,
- increasing incidence of chloroquine-resistant *P. falciparum* malaria. (Ayyamni and Chee, 1988)

Arasu (1992) reviewed a number of reports and information from Malaysian sources which "were analyzed according to the different behavior/determinants favoring occurrence of malaria in the country [Malaysia]."

- Estates that have just been cleared for replanting favor the breeding vectors,
- Workers stay in temporary houses in the vicinity of these scheme,
- Illegal immigrants [arrive] already infected with malarial parasites,
- Habit of relaxing at dusk outside,
- Orang Asli,
- Breeding of the vector *Anopheles sundaicus* [on coastal islands]
- Non-use of mosquito nets,
- Non-compliance to the full duration of treatment with anti-malarials [drug treatment],
- Bitter taste of anti-malarial drugs,
- Failure to seek early treatment for malaria: illegal immigrants (fear of being apprehended), Orang Asli (nomadic lifestyle), traditional medicines (sought before other treatment),
- Impossibility of screening and follow-up of incoming illegal immigrants, part-time and mobile rural workers,
- Lack of recognition of malaria as a serious health problem among afflicted,
- Ineffective focal spraying after case detection,
- Flimsy, temporary, or otherwise unsuitable structures for spraying,
- Customs and beliefs prohibit house-spraying or drug treatment,
- Health education ineffective due to language problems,
- Anti-larval measures not possible or appropriate,
- Frequent mobility of immigrant workers, Orang Asli,
- Asymptomatic malaria favors transmission. (Arasu, 1992)

In short, these epidemiological conditions provide a rationale for the continued transmission of malaria, but are less useful for explaining all the epidemiological variation that exists over time and space. As all of these conditions have existed from the beginning of the MEP (except chloroquine-resistance), they also imply that *status*
quo interventions are unlikely to achieve sufficiency, unless longstanding conditions change.

Variation of malaria transmission in Malaysia exists from macro scale (the wide difference in incidence between Sabah and Sarawak, two neighboring states; the large seasonal and inter-annual incidence variations) to smaller scale (absence or presence of malaria transmission in neighboring villages, or houses within a village). Investigation of microvariations (UNDP/World Bank/WHO, 1985) is difficult but important for identifying determinants that may have only a particularistic (Miettinen, 1985) importance within a specific geographic and temporal locality, but critical relevance to an intervention strategy.

Past malaria field research concentrated on survey studies of descriptive epidemiology, vector bionomics relevant to insecticide application, or intervention studies of insecticide application or chemoprophylaxis. Meanwhile, many of the variables that relate malaria transmission to human behavior were left unstudied (Dunn, 1979). A WHO survey of field research in malaria stated,

"As indicated by the number and proportion of abstracts, amounting to one-third of the total in this inventory, the scope of field research carried out in South-East Asia has been very extensive, covering the majority of research areas. However, studies on the community in respect to participation and to malaria morbidity, on personal protection and on environmental control methods appear to have been largely overlooked." (Haworth, 1984)

Furthermore, the WHO/TDR Program noted that "case-control studies have been little used in research on tropical diseases..." (UNDP/World Bank/WHO, 1985)

The advantages, in economy of time and expense, of the case-control approach need to be applied to malaria research.

Variability within a geographic area such as Kelantan can be scaled at the state, district, village, or individual level, e.g., seasonal variation, coastal vectors with
different bionomical characteristics from forest vectors, village populations with
different behaviors from land-scheme populations, or variable risk of malaria infection
among apparently similar inhabitants of a village.

Published research on the malaria problem in Malaysia has described
epidemiological conditions that frustrate the accomplishment of eradication or control,
in spite of the best efforts of the control program. Meanwhile, epidemiological
research opportunities exist.

There is little investigation of the most important variable, climate and rainfall.
Second, behavioral and environmental factors are longstanding items on the case
investigation form, but are never used for analysis or intervention, partly because there
is no reference/control data (no denominator data from non-cases), and partly because
it is assumed to be non-informative. Third, the vast amount of routine operational data
from the control program (e.g., biodata on blood-films collected and positives detected)
is largely untapped.

To summarize:
· Much research activity on malaria, but little progress on malaria control.
· Much epidemiological description of malaria, but few risk factors or
determinants.
    · lack of research on variation
    · assumption of homogeneous risk
· Rainfall and climate effects ignored.
· Lack of denominator data in the operational data:
    · age- and sex-specific incidence not closely examined due to lack of
denominator (lack of non-case data)
- common risk factors on case investigation form are not used for analysis, due to lack of denominator (lack of non-case data).
CHAPTER 2: LITERATURE REVIEW

MALARIA PARASITE AND DISEASE

Malaria is caused by protozoan parasites that reproduce and multiply in a complex life cycle partly occurring in a vertebrate host and partly in a mosquito vector. Disease symptoms are caused by the blood-borne phase of the parasite.

There are four species of malaria parasites that infect humans (many other malaria species infect other vertebrates, including birds, reptiles, rodents, large mammals, and hominids). The four human species are *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*. *P. falciparum* and *P. vivax* are the most common of the four and usually found in all malarious parts of the world. *P. malariae* and *P. ovale* are the rarer species.

The mosquito vector is always genus *Anopheles*, but vector species vary between localities with malaria transmission. Vector attributes (bionomics) vary greatly by species leading to completely different transmission characteristics and vectorial capacity: type of preferred water for breeding site; seasonality; host preference; time of feeding; site of feeding; susceptibility to infection; susceptibility to insecticides, repellents, and other irritants; vigor and probability of survival.

Lifecycle and Parasitology

The lifecycle in the mosquito (extrinsic) is morphologically similar in all four malaria species. Microscopic speciation of the various stages (ookinete → oocyst → sporozoite) is not possible, but there are species-specific surface antigens. After a
multiplication stage in the mosquito gut, the human-infective sporozoite migrates to the mosquito salivary gland. This extrinsic cycle is 1-5 weeks, dependent on environmental temperature and species, but tends to be shorter in *P. falciparum* than *P. vivax*. Development of *P. vivax* can occur at lower minimum temperatures than the other three species, thus leading to vivax transmission at higher altitudes and in temperate climates.

The lifecycle in the human host (intrinsic) begins with injection of sporozoites into the bloodstream, by the feeding female anopheline mosquito, which quickly localize in liver cells (hepatocytes). This primary exoerythrocytic cycle is similar in all four species leading to multiplication (schizogony) and release of merozoites into the blood. However, in *P. vivax* infection, some sporozoites do not develop directly into tissue schizonts, rather transform into a dormant stage called hypnozoites. Hypnozoites remain latent in hepatocytes for varying periods of time and then develop in a secondary exoerythrocytic cycle leading to tissue schizonts and release of merozoites. This is the cause of *P. vivax* relapse. *P. ovale* also relapses, but a hypnozoite has not yet been demonstrated. *P. falciparum* and *P. malariae* have no hypnozoite stage, no secondary exoerythrocytic cycle, no relapse; however, erythrocytic parasites can persist, due to treatment failure, leading to recrudescence.

Mature tissue schizonts rupture releasing merozoites into the bloodstream to infect and multiply asexually in red blood cells (RBCs). Erythrocyte invasion is dependent on specific receptors: in *P. vivax* the Duffy receptor, in *P. falciparum*, glycophorin. Genetic resistance to *P. vivax* infection exists in many individuals of West African descent (who lack Duffy factor). Other genetic factors (sickle cell,
thalassemia, G-6-PD deficiency) are associated with intracellular mediation of malaria infection.

The prepatent period in *P. vivax* and *P. falciparum* is approximately 6-9 days. Though the incubation period to first clinical symptoms may be up to 35 days, it tends to average 12 days in *P. falciparum* and 14 days in *P. vivax*.

Erythrocytic schizogony takes about 48 hours in *P. vivax* and *P. ovale*, slightly less, about 46-48 hours, in *P. falciparum*, and 72 hours in *P. malariae*. Asynchronous symptom patterns during the early phase of infection are common, then *P. vivax* tends to develop synchronous cycles of schizogony, while *P. falciparum* tends to remain asynchronous. Each cycle of erythrocytic schizogony releases merozoites into the blood which reinfect RBCs perpetuating the infection. The duration of untreated infection with spontaneous cure is estimated to be one year for *P. falciparum* and three years for *P. vivax*.

Some erythrocytic schizonts develop into gametocytes, the mosquito-infective stage. Gametocytes of *P. vivax* appear in the peripheral circulation about 3 days following other stages, whereas in *P. falciparum* gametocytes appear about 12-14 days later. If taken up in a bloodmeal by a susceptible anopheline species, extrinsic development begins anew.

Pathology

Anemia is a common feature of all malaria due to RBC destruction. *P. falciparum* infects all stages of erythrocytes, whereas *P. vivax* infects only reticulocytes and *P. malariae* infects only older RBCs. Thus *P. vivax*, *P. malariae*, and *P. ovale* tend to be self-limiting disease with lower parasitemia and less erythrocyte destruction,
while *P. falciparum* infection is a medical emergency that can quickly lead to death. *P. falciparum* also commonly multiply-infects RBCs. In the terms of evolutionary hypothesis, the three more benign species seem well-adapted to the host, i.e., do not cause serious mortality.

*P. falciparum*-infected RBCs tend to sequester in the deep vasculature during erythrocytic development. This explains the diagnostic observation of only young ring-stage trophozoites in the peripheral blood-film. *P. falciparum*-infected RBCs have microscopically observable adherent surface knobs. Experimental work has demonstrated an enzyme-susceptible receptor on *P. falciparum* and not *P. vivax*, that is adherent. This stickiness leads to congestive complications in various organs, e.g., cerebral malaria, where the brain's circulation is impaired by sludging of malaria-infected RBCs; also renal, splenic, or hepatic failure. *P. falciparum* also causes pulmonary edema. Sequestration in the placenta of malaria-infected pregnant women is a serious problem leading to poor fetal development or even abortion. Immunosuppression is under study as a poorly understood complication of pregnancy and malaria that leads to maternal mortality.

**Chemotherapy**

*P. falciparum* is widely drug-resistant, greatly complicating chemotherapy. Chloroquine-resistant *P. falciparum* (CRPF) in now virtually global, although some foci of susceptibility remain, and chloroquine may be useful against CRPF in some immune populations. Where frank CRPF exists, sulfadoxine-pyrimethamine is used, where resistance to this combination has emerged, mefloquine is used. Except in Thailand and neighboring countries, an extended regimen of quinine-tetracycline is
curative. Halofantrine and artemisinine are two alternative schizontocides that have come into use. Primaquine is prescribed in endemic *P. falciparum* areas as a gametocytocide to reduce the transmission potential of infected individuals.

Although some foci of chloroquine-resistant *P. vivax* have been reported, *P. vivax* is still widely susceptible to all blood schizontocidal drugs, in particular chloroquine which is usually prescribed 1500-1800 mg, divided over 5 days, with a loading dose on day 0. This will clear all erythrocytic stages. However, all blood schizontocides are ineffective against the latent hypnozoites, therefore, primaquine is prescribed either in a 14-day regimen or a 8-week regimen. In areas of endemic transmission, the utility of radical curative vivax treatment is often questioned, thus primaquine treatment may be reserved for those who visit and then permanently leave transmission areas.

Chemoprophylaxis is still feasible with chloroquine against all species other than *P. falciparum*. However, *P. falciparum* prophylaxis is very unsatisfactory at present and requires specific information about drug susceptibility of local geographic strains. In many cases today, the only feasible advice is to practice antimosquito protection.

**Immunology**

Malaria immunology is an area of vigorous, active research due to the need for a vaccine. Repeated malaria infection leads to protective, though non-sterilizing, immunity called premunition. This immunity is lost when the stimulus of repeated infection is removed.

Immunity to malaria is both species- and stage-specific, one of several complications to an effective vaccine. Sporozoite-, gametocyte-, and merozoite-
specific immune research has progressed. A sporozoite vaccine would protect against
the mosquito-injected stage preventing or limiting initial infection in the liver. A
merozoite vaccine would attack the erythrocytic stage limiting reinfection of RBCs. A
gametocyte vaccine would promote a unique form of 'altruistic' immunity, wherein
immunity in the human host would produce antibody to attack the gamete in the
mosquito gut, thus interrupting the transmission cycle.

Human efficacy trials of the sporozoite vaccine were disappointing. Field trials
of merozoite vaccines are in the early or middle stages. The Colombian vaccine project
led by Patarroyo has reported positive results, followed-up by qualitatively mixed
results in African field trials.

MALARIA ERADICATION AND CONTROL

The history of antimalaria intervention before 1945 is largely the sanitation of
vector breeding sites through drainage, filling, and larviciding (with Paris green or oil).
Quinine was used for centuries as a curative and prophylactic drug until the synthesis of
atrabrine, chloroquine, and other antimalarial drugs (starting in the 1930s) expanded the
pharmacopia.

After 1945, DDT and other synthetic pesticides came into use for larviciding
and residual intradomiciliary insecticiding. Regular application of insecticides resulted
in sensational reduction of malaria incidence. The inadvertent interruption of the
application cycle revealed that malaria could be eradicated without eradicating the
mosquito--anophelism without malaria. Those mosquitoes feeding on humans came
under selection pressure by entering sprayed houses. This selective reduction of vector
longevity broke the cycle of human-to-human transmission. Eradication of the parasite reservoir in humans could occur without eradication of the vector mosquito.

In the 1950s, a few such successes propelled the idea of malaria eradication into a global campaign, based on residual insecticiding coupled with surveillance and follow-up drug treatment. Mathematical modeling (by Ross, Macdonald, later by Garrett-Jones, Dietz and Molineaux) offered a theoretical rationale for a time-limited campaign. Modeling demonstrated that transmission dynamics could be explained by the basic reproduction rate (number of new infections that can be propagated by a mosquito) and, in slightly simpler form, vectorial capacity:

\[
\text{Vectorial Capacity} = m \times a^2 \times \frac{p^n}{-\ln(p)}
\]

- \(m\) = mosquito density (# mosquitoes biting human/day)
- \(a\) = human-biting rate (# humans bit/mosquito-day)
- \(p\) = probability (daily) of mosquito survival
- \(n\) = # days for sporozoite maturation in mosquito

Three major factors interact: vector mosquito density (relative to human host), the daily human-biting rate of the vector (assumed to be once per 2-4 days, depending on gonotrophic cycle of egg maturation), and vector survival (expectation of life over the period necessary for parasite development in the mosquito).

The important realization was that reduction of vector longevity, specifically by killing human-feeding mosquitoes in insecticide-sprayed domiciles, could theoretically reduce the basic reproduction rate below the break point at which transmission dies out.
The availability of long-acting residual insecticides made indoor residual spraying designed to alter vector longevity seem a propitious intervention strategy.

The described factors, resting on many contributing factors (biologic and non-biologic), also rest on an assumption of homogeneity of malaria transmission risk and randomness. Research has demonstrated that malaria transmission is more non-random than expected, e.g., Burkot (1988) described non-random host selection by mosquitoes. Experience has shown the theory has problems.

By the 1960s, it was apparent that time-limited malaria eradication would not be achieved. Residual intradomiciliary insecticiding failed as a universal interdiction to malaria transmission. Empirical experience revealed that many vector species were sufficiently plastic or adaptive to frustrate the eradication theory, and the necessary high level of spraying efficiency was impossible to attain in operational conditions.

During the 1970s, most malaria eradication programs around the world were recast as malaria control programs. This semantic change had the broad implication of lifting the urgency to attain a near-term goal through a military-like public health campaign, even though eradication remained an explicit long-term goal. In practical terms, the operational tactics of house-spraying, larviciding, surveillance, house-to-house canvassing, mass drug administration, microscopic diagnosis, entomological field monitoring continued largely intact in many national programs.

In the 1980s, shrinking health budgets motivated health ministries to integrate the so-called vertical programs, such as malaria control and tuberculosis control, into the general health infrastructure. Malaria control activities were consolidated into multi-disease control programs, and malaria staff were redefined as multipurpose health workers.
MALARIA CONTROL TACTICS

Malaria control strategy seeks to reduce morbidity and mortality through a variety of tactics or operational activities. These generally include residual house-spraying, detection and treatment of cases, surveillance for disease outbreaks, and surveillance of mosquito vectors.

Insecticiding

Residual intradomiciliary spraying: the application of long-acting insecticides, such as DDT, BHC, dieldrin, malathion, fenitrothion, on the interior surfaces of houses and other structures in order to kill those mosquitoes that feed on humans. Many species rest before or after feeding, which provides the rationale for residual spraying.

Fogging and ultra low volume (ULV): Fogging spreads a cloud of insecticide that knocks down flying or resting mosquitoes. One type of fogging machine vaporizes insecticide in kerosene solution by heat. The second type, ULV, emits microscopic particles by forcing a small volume of concentrated insecticide through a shearing nozzle. Both fogging and ULV machines can be either handheld or truck-mounted. Fogging reduces vector density during outbreaks.

Larviciding

Each species of mosquito lays eggs, which hatch into larvae, in a particular and characteristic body of water. When a vector species breeds in identifiable bodies of standing or slow-moving water, application of anti-larval chemicals may be appropriate
for density reduction. The most common agents in use are: temephos (Abate), *Bacillus thuringiensis israeliensis* (Bti), and oil. In earlier decades, Paris green was used, and some synthetic insecticides (halted due to environmental hazard). A great many malaria vector species breed in water that is unsuitable or unfeasible to larvicide.

**Case Detection/Surveillance**

**Passive Case Detection (PCD):** Refers to blood-films collected from presenting patients at hospitals, clinics, and other static health posts.

**Active Case Detection (ACD):** Refers to blood-films collected by house-to-house canvassers who travel a regular circuit. The canvasser usually elicits a recent history of fever, or other suspicion of malaria, before taking the blood-film.

**Mass Blood Survey (MBS):** Refers to blood-films collected in a time-limited survey from all inhabitants of a geographic locality, regardless of symptomatology. MBS may be carried out either on a regular or extraordinary basis.

**Investigational Survey:** Refers to blood-films collected in the course of an outbreak investigation. A case of malaria detected in areas of low or no malaria transmission triggers an outbreak investigation. If, in the course of the investigation, a suspicion of local transmission arises, then possible secondary contacts are blood-filmed.

**Drug Treatment**

**Curative treatment:** Drug-resistant strains of *P. falciparum* have complicated the treatment of malaria. In simpler days, chloroquine was the drug of choice,
effective against all four species of malaria. Now specific knowledge of local strain susceptibility is necessary to prescribe effective medication.

**Prophylaxis:** Antimalarial drug is taken on a regular schedule in a preemptive bid to prevent or cure infection before symptoms appear.

**Mass Drug Administration (MDA):** Refers to distribution of antimalarial drugs on a population basis in defined localities to reduce the parasite reservoir without bothering to diagnose parasitemia. MDA leads to selection for drug-resistant malaria strains.

**Personal Protection and Health Education**

Many malaria control programs now promote and distribute bednets to reduce human-vector contact. Research has demonstrated an enhanced effectiveness when bednets are treated with permethrin or other insecticides. Health education is carried out to inform and promote personal protection against mosquitoes, e.g., repellents, house-screening, house-siting.

**Entomological Surveillance**

Malaria control programs periodically sample vector densities to monitor the effect of anti-mosquito measures. Wild-caught mosquitoes are tested to monitor insecticide susceptibility.

**Larval survey:** Larvae are sampled by dipping using a long-handled ladle following a defined protocol to ensure uniformity of technique in monitoring change in density.
Adult survey: Animal-baited traps (e.g., a goat or water buffalo) attract mosquitoes which are collected and counted following a defined protocol to monitor change in density.

Human-biting catches use a human as bait. Either the collector catches the mosquitoes biting himself, or a collector catches them off a resting bait.

Light traps attract mosquitoes towards a light and draw them into a cage, either with one-way baffles or a small fan.

Insecticide-susceptibility: Wild-caught mosquitoes are held in small cages that force them to rest on insecticide-treated papers. Percentage mortality is determined in comparison to control (untreated paper).

MALARIA RESEARCH IN MALAYSIA

Malaria research and control has a long history in Malaysia. Sir Malcolm Watson initiated in 1901, in Port Swettenham, one of the first examples of successful malaria control when he engineered bunds with flap/sluice valves, and drainage, to reduce malaria transmission (Moorhouse, 1965). The brackish-water vector An. sundaicus was later identified. Watson used jungle-felling and drainage to eliminate breeding sites of shade-loving An. umbrosus, but that strategy amplified breeding of sun-loving An. maculatus (De Las Llagas, 1985).

Annual VBDCP reports review the status of malaria and malaria control in Kelantan, with some description of the general epidemiology of malaria (e.g., Rancangan Basmi Malaria Kelantan, 1972; VBDCP Kelantan, 1983; VBDCP Kelantan, 1984; VBDCP Kelantan, 1991a). These reports list various reasons for the status of continued incident malaria cases, but these are difficult to interpret as risk-factors. In
1990, the factors associated with increased number of malaria cases were (VBDCP Kelantan, 1991a):

1. Opening of new land schemes with undocumented workers who are difficult to track.
2. Poor liaison and cooperation from contractors that bring in foreign workers.
3. Difficult logistics coupled with lack of knowledge, attitudes and practices (KAP) in village population towards malaria prevention.
4. Inclusion of various Orang Asli (aborigine) localities in the VBDCP area of supervision.
5. Imperfect radical treatment of confirmed cases.
6. Population movement between Malaria-free, Malaria-prone, and Malaria-problem areas.
7. Possibility of drug-resistant malaria in population groups in interior areas.

Peninsular Malaysia

Published epidemiological research on malaria in Malaysia is surprisingly sparse. Mentioned previously were Mak et al. (1992), Ayyamni and Chee (1988), Arasu (1992), and Riji (1992). Rahman (1982) published an earlier general overview.

More recently Rahman et al. (1993a) reported on monthly malaria incidence in a village and An. maculatus density which showed positive correlation, while vector density showed negative correlation with rainfall, which was explained by washing out of larvae during heavy rain. Rahman et al. (1993b) also reported on monthly density of An. aconitus, a suspected vector. This species also showed negative correlation with rainfall.

Population mobility is listed as an important obstacle to successful implementation of the current anti-malaria strategy. Sornmani et al. (1983) studied migration in Thailand, but Malaysia has not been studied.
Kelantan

Tay (1987) surveyed knowledge, attitudes, and practices (KAP) to malaria in the general area of Gua Musang and presented descriptive results. There were no comparison groups. The entire area was assumed to be a uniformly malaria-endemic region without variation. Description of the sampling methodology is sparse, making it difficult to interpret the results.

Hamzah et al. (1989) compared KAP to malaria in two villages of high and low incidence. This study identified personal protective measures as an important difference. The study acknowledged some non-comparability between the two study sites, as well as the exclusion of factors such as vector population, human mobility, and other epidemiological parameters. There was zero malaria incidence (no transmission) in the "low incidence" village. Thus risk of malaria was non-comparable in the two villages.

Hamzah and Izzuddin (1990) reviewed three major groups with malaria risk in Kelantan, provided some descriptive analysis, and offered some prescriptive recommendations for further work.

There has also been a major intervention study of insecticide-impregnated bednets in Kelantan by the VBDCP (Hamzah et al., 1988; Hii and Palmer, 1989), which reported some success.

Riji (1992) describes a Primary Health Care approach for malaria control that was initiated in Sarawak and later started in Kelantan, involving health workers and community members in village-level early diagnosis of malaria, but the article deals primarily in broad terms.
Sabah

Other epidemiological malaria research has been published from Sabah. Hii and colleagues (Hii et al., 1985a; Hii et al., 1985b; Hii et al., 1988) have carried out epidemiological surveys in Banggi Island and Upper Kinabatangan. An epidemiological survey of filariasis and malaria in Banggi Island and Upper Kinabatangan, Sabah, revealed microfilarial rates of 7.2% and 8.6% respectively and malaria prevalence of 9.7% and 16.9% respectively. Ratios of falciparum: vivax: malariae were 1:1:0.17 and 1.4:1:0.12 for Banggi and Upper Kinabatangan respectively. *Anopheles flavirostris* was incriminated as a new malaria vector in Banggi (primary malaria vector is *An. balabacensis*). Using 1) all-night human-bait collections of anopheline species from inside and outside houses, and 2) buffalo-biting and CDC light-trapping catches, they calculated vectorial capacity (number of infections distributed per case per day) during March and November 1984. Using the dissection technique, confirmed by the immunoradiometric assay (IRMA), more sporozoite-positive infections were detected in *An. balabacensis* and *An. flavirostris* in November than in March (*P. falciparum* sporozoites were confirmed by IRMA). An average of 76.2% of the *An. balabacensis* population survived long enough in November to be potentially infective with *P. falciparum*. The human biting rate was low (less than 5 mosquitoes/human/night), but highly anthropophilic feeding and high anopheline life expectancy contributed to high estimates of falciparum malaria vectorial capacity.

Collett and Lye (1987) also analyzed epidemiological data from Banggi Island. Baseline epidemiological and entomological data from three villages were used to model malaria transmission using a non-seasonal version of the deterministic model of Dietz, Molineaux and Thomas. The basic model described observed prevalence rates
of falciparum parasitemia, and a modified model was used to simulate mass chemotherapy with various combinations of schizontocidal and gametocytocidal drugs.

Leake and Hii (1989) surveyed KAP related to malaria transmission and bednet use in two areas of Sabah. Treatment failure with Fansidar was reported in Sabah by Tan and Tan (1983; 1984).

Serological Studies-Peninsular Malaysia

Several serological surveys of malaria in Malaysia have been published, establishing that antibody levels and parasitemia are related to age. Thomas et al. (1981) surveyed 143 out of 190 Orang Asli children in an Ulu Kelantan site. P. falciparum and P. vivax were detected. Prevalence of three indices were compared: IFA (P. falciparum) positive, 84.6%; enlarged spleen, 81.8%; parasite positive blood-film, 43.4%. Age-specific patterns of the three indices showed positive correlation up to age 9 years, after which older children showed a rise in antibody titer with drop in spleen and parasite prevalence, indicating a hyperendemic transmission environment.

Mathews and Dondero (1982a) carried out cross-sectional surveys at 4-week intervals for a year comparing IHA titers to parasitologic results in an endemic population of Malaysia. Seropositivity rates showed positive correlation with age and number of malaria episodes in young children. IHA antibody titers showed variability that "tended" to vary with parasitologic results. Mathews and Dondero (1982b) were also able to follow 62 persons in the study longitudinally by IHA serology and blood-film. IHA titer variation in the group correlated with parasitologic results, but did not hold up within individuals. Chemotherapy was suggested as an immune response modulator.
Mak et al. (1987) surveyed IFA titer and parasite prevalence in two adjacent populations, Orang Asli and Malay. In the Orang Asli, age-specific parasitemia was highest in 0-4 years, declining to zero in 30-39 years. In the Malay, age-specific parasitemia increased with age. Age-specific IFA titers (\textit{P. falciparum} and \textit{P. cynomolgi}) showed inverse correlation with parasitemia in Orang Asli. Age-specific IFA titers in the Malay also increased with age, but were much lower than in the Orang Asli. ELISA antibody levels were similarly high in Orang Asli and low in Malay. They concluded that malaria transmission was much higher in Orang Asli leading to a higher level of protective antibody as compared with the Malay population.

Gordon et al. (1991) studied epidemiological, parasitological, and entomological characteristics over a 16-week period in an Orang Asli population. They confirmed previous observations that age-specific parasite prevalence decreases with age, while circumsporozoite (CS) antibody increases with age. \textit{An. maculatus} had a sporozoite rate of 2\%, and an estimated inoculation rate of 0.3 infectious mosquito bites per person per month for \textit{P. malariae}, 1.2 for \textit{P. falciparum}, and 2.4 for \textit{Plasmodium vivax}. There appeared to be some resistance to infection associated with high baseline ELISA titer to \textit{P. falciparum} CS protein.

Finally, Archibald (1991) et al. compared IFA, ELISA, parasite rate, spleen size, and age in an Orang Asli population in Pahang state. These variables indicated a population facing meso- to hyper-endemic malaria, with parasitemia and concomitant immunity rising with age in 0-4 year olds, reaching a plateau in 5-9 year olds, and then immunity continuing high into adults and suppressing parasitemia. ELISA titer and spleen size increased with age, while parasite rate declined. IFA titer was consistently high and unvarying in relation to other variables, including age.
Entomological Studies

Entomological studies in Malaysia have been reviewed by Vythilingam et al. (1992). Field studies over many decades have incriminated *An. maculatus* as the principal vector in Peninsular Malaysia, with only form E of the species complex found in Malaysia (Loong, 1988). Less important vectors, due to limited distribution, are *An. sundaicus*, *An. campestris*, *An. leiifer*, and *An. dirus*.

*An. maculatus* breeds in slow flowing streams and seepages with direct sunlight exposure. The female feeds preferentially on cattle compared to humans. It rests outdoors and attacks humans on entering the house. Biting activity occurs the night-long with a major peak around midnight. Monthly sporozoite rates have been found high (0.38-5.08%) and high survivorship (p=0.821-0.962) indicates a highly efficient vector (Loong et al., 1988). Despite decades of DDT residual house spraying, *An. maculatus* remains susceptible, because of the excito-repellent effect of the insecticide (Loong et al., 1989).

Drug-resistance Studies

Drug-resistant malaria is prevalent in Malaysia. In 1950, proguanil-resistant *P. falciparum* was confirmed (Edeson, 1950). In 1952, proguanil-resistant *P. vivax* was confirmed (Wilson et al., 1952). During the 1960s, chloroquine-resistant *P. falciparum* was confirmed in several locales (Montgomery and Eyles, 1963; Sandosham et al., 1966; Andre et al., 1972; Dondero et al., 1975; Dondero et al., 1976; Ho et al., 1987). Fansidar-resistance was confirmed in the early 1980s (Black et al., 1981;
Ponnampalam, 1982). Chloroquine-resistance in Sabah was confirmed during the 1970s (Rahman, 1980).

CASE-CONTROL STUDIES ON MALARIA

Foo et al. (1992) used a study of matched pairs of Malayan aborigines (Orang Asli) to demonstrate that ovalocytosis protects against malaria infection. Non-hemolytic hereditary ovalocytosis occurs at high frequency in Orang Asli. This appears to result from reduced susceptibility of affected individuals to malaria. That study followed from Mohandas et al. (1984) who demonstrated that ovalocytes are a barrier to malarial invasion in vitro. There is a case-control study from Malaysia examining a possible association of malaria infection with nasopharyngeal carcinoma (Yadav, 1984).

Case-control studies on malaria transmission have not yet been carried out in Malaysia. They have been carried out in Thailand, the Philippines, Brazil, Bangladesh, and Sudan:

Fungladda and Sornmani (1986) reported on determinants of malaria positive patients in a case-control study, using malaria clinic patients as a study base. Cases and controls were matched on age and sex, but not on place of infection, i.e., resident in same village. In other words, they assumed a homogenous risk of mosquito bite among patients presenting at the clinic. They identified an association between malaria infection and several risk factors.

Fungladda et al. (1987) used a hospitalized study base to identify risk factors of malaria. Since they did not match for place of infection, this means the risk of infection could have been noncomparable.
Butraporn et al. (1986) reported a pair-matched case-control study using a questionnaire to gather information on a set of variables affecting malaria transmission. Multiple logistic regression analysis was used to identify and incriminate various indicators such as stability of residence, education, family income, forest-associated travel or work, and proximity of vector breeding sites.

Sawyer (1986) reported on a longitudinal study with nested case-control studies of settler families in Amazonian Brazil. Multivariate analysis based on a broad range of economic, social, cultural, political, entomological, parasitological and serological studies led to suggestions for concentrating limited resources, based on predictions of socioeconomic and ecological variables, to a targeting strategy, e.g., sanitation in urban areas, mass blood-film surveys for asymptomatic hosts in gold mining areas. He also advocated community involvement and personal protection.

Lariosa (1986) studied determinants of malaria in a Philippine locality but with equivocal results.

El Samani et al. (1987) reported the association between nutritional, environmental, and sociodemographic factors, and malaria occurrence among children in a rural Sudanese community.
CHAPTER 3: MATERIALS AND METHODS

A primary source of data for this study was operational records and files of the VBDCP Kelantan headquarters office in Kota Bharu, Kelantan. All summary data on monthly number of blood-films collected and malaria cases detected in Kelantan State came from monthly and annual records and files at this site. Additional information was collected from interviews with staff of the VBDCP, and site visits during the course of the field study. All data on monthly rainfall came from monthly summary reports of Department of Meteorology Malaysia (1970-91), or from Department of Drainage and Irrigation Kota Bharu (1992). All raw data used in the analysis of risk groups by blood-film collection source in Gua Musang District came from VBDCP logbooks and record-sheets retrieved from the VBDCP office storerooms, Gua Musang, Kelantan. The blood-film biodata and results were transcribed to computer database by the candidate and an assistant. All case-control data in Kampung Jerek, Bertam District, Kelantan, were collected by the author and an assistant.

Population census data came from three sources: 1) final reports of the 1980 National Census (Department of Statistics, 1983), 2) preliminary reports of the 1991 National Census (Department of Statistics, 1991), and 3) unpublished annual reports of the VBDCP Kelantan (which use population estimates for districts and sectors, received from the Department of Statistics Malaysia).
STUDY SITE

Kelantan, one of the thirteen states of Malaysia, is located in the northeast corner of Peninsular Malaysia (Figure 2), bordering Thailand at the north, the South China Sea at the east (approximately 70 km. of sea coast), and sharing borders with three other Malaysian states (Perak, Pahang, Trengganu). Kelantan area is 14,943 sq.km. A flat coastal plain rises to hills and forested mountains in the interior.

The 1991 Kelantan census population was 1,181,680. Ethnicity in Kelantan is dominantly Malay (95%), with minorities of Chinese, Thai, Indian, and aborigine (Orang Asli). It is one of the poorer states of Malaysia, with the main economic activities being timber and agriculture (rice, tobacco, rubber, palm oil).

Malaria has long been prevalent in Kelantan, but has receded from the urban and coastal areas of the state. This is explained in part by specific antimalaria interventions (antilarval drainage, residual intradomiciliary insecticiding, and case surveillance), and also to socioeconomic development trends (general improvements in housing, health care, and living standards).

Gua Musang District

Gua Musang District is the largest but least populous of Kelantan State's nine districts (Table 1). Gua Musang District is divided into three Sectors (one of which is also called Gua Musang). The district is located in the interior of the state where the terrain is hilly, rising to forested mountains. There is both small-scale farming (rice, tobacco, rubber small-holdings, fruit) and large plantation developments of palm-oil, as well as timber-felling. Timber and plantation development attract large numbers of
young, single male laborers, both Malaysians and economic migrants from neighboring countries.

**Antimalaria Administrative History**

A Malaria Pilot Project (1960-64) in Peninsular Malaysia, and a nationwide malaria survey (1965-66), led to the initiation of a Malaria Eradication Program (MEP) in 1967. MEP activities began in Kelantan in 1969, following a WHO model of Preparation Phase (1 year), Attack Phase (4 years), Consolidation Phase (3 years), and finally Maintenance Phase (VBDCP Kelantan, 1983).

By 1978 (9 years later), only 12 of 20 Kelantan sectors had entered Consolidation phase, while the remainder of the state was still in Attack phase. None were in Maintenance phase (VBDCP Kelantan, 1984). Failure to achieve time-limited eradication was observed in other states of Malaysia, as well as other countries in the region. This led to reevaluation and redefinition to a malaria control program, i.e., continuation of the antimalaria interventions, but without a time-limit.

Another series of administrative actions occurred during 1982-85: merging of the antilarval services, the malaria control services, and the dengue and filariasis control services into the Vector-Borne Diseases Control Program (VBDCP), encompassing those diseases, plus Japanese B encephalitis, typhus, plague, and yellow fever. This change integrated the 'vertical' malaria control program into a component of the medical and health services with broader responsibilities.

During the 1980s, some coastal sectors were declared malaria-free (i.e., in Maintenance phase). In 1986, classification terminology was officially revised:
Districts and Sectors (district sub-units) defined in 1991 as Malaria-Problem, Malaria-Prone, or Malaria-Free are listed in Table 1 and illustrated in Figure 3.

Current VBDCP Operations and Procedures

As of 1991, the VBDCP Kelantan carried out the following routine, operational activities: residual intradomiciliary DDT spraying; passive case detection in hospitals and clinics; active case detection by VBDCP canvassers; mass blood surveys and contact surveys by VBDCP canvassers; case surveillance, investigation and follow-up; entomological surveillance; reference laboratory diagnosis and checking. Larviciding and drug-resistance testing are carried out on an extraordinary basis.

Insecticiding

Residual intradomiciliary DDT spraying on a twice-annual schedule (every six months) is carried out in the Malaria-Problem sectors of Kelantan by teams of spraymen. If malaria transmission is determined to occur in a Malaria-Free or Malaria-Prone locality, then focal spraying of houses is carried out.

Case Definition

A malaria 'case' in Kelantan is defined by a parasite-positive blood-film (using a blood drop that is spread, fixed, and Giemsa-stained on a glass microscope slide).
All medical and health facilities have a diagnostic laboratory on-site, or nearby, where microscopic examination by trained technicians determine positivity, parasite speciation, and parasite density of blood-films collected.

This is not to say that duplicate or follow-up blood-films of the same case are counted twice. As far as possible (e.g., when the patient is hospitalized, or returns to the same medical facility, or the case is investigated), the VBDCP staff censor duplicate blood-films from the same patient, according to a simple and standard protocol: repeat *P. falciparum* within 30 days is counted as a recrudescence, repeat *P. vivax* within 6 months is counted as a relapse.

**Blood-film Collection**

Blood-films are collected by the three different methods (please note, terminology and abbreviations are standard VBDCP usage):

**Passive Case Detection (PCD):** patient presents at hospital or clinic with illness and symptoms; blood-film is examined.

**Active Case Detection (ACD):** VBDCP field canvasser conducts house-to-house visits and takes blood-film from person with recent fever, or otherwise suspected of having malaria, based on interview.

**Investigation (INV):** blood-films collected through mass blood surveys (MBS), or contact surveys in locality of recently confirmed malaria-positive infection(s).

In practice, each method may have a different probability of detecting a positive patient. PCD relies on a clinically ill patient to present to a hospital or clinic, and thus the probability of malaria may be greater. PCD tends to be independent of staff work patterns. INV collects blood-films from asymptomatic persons, thus the probability of
a negative blood-film is higher, while ACD collects blood-films from people with a
history suggestive of malaria. Both ACD and INV blood-film collection are affected
by factors such as major holidays (e.g., the Muslim fasting month of Ramadan) and
high rainfall which leads to flooding and may limit staff work activities.

Malaria blood-films are recorded in logbooks or on data-sheets with the
following biodata: date of blood-film, name, age, sex, village, parasite species
diagnosis, parasite density (qualitatively graded from 1 to 4, according to VBDCP
protocol). These data are used to compile weekly, monthly, quarterly, and annual
summary reports.

**Surveillance and Follow-up**

It is standing policy in Kelantan to investigate all malaria cases to determine
origin of infection. A standard interview determines when and where transmission
occurred based on domicile and travel of the patient in relation to incubation period. In
practice, all cases detected in Malaria-Free and Malaria-Prone areas are investigated, as
are most cases in Malaria-Problem areas, the difference being the feasibility and
possibility of tracking illegal and/or migrant laborers in the Malaria-Problem areas. If
transmission is determined to occur in a Malaria-Free or Malaria-Prone area, then
follow-up remedial measures include INV surveys and anti-mosquito spraying.

**Incidence**

The Kelantan VBDCP collects and reports a substantial amount of malariologi-
cal data. Population denominators are only used to calculate the Annual Parasite
Incidence rate (API = total number of positive blood-films divided by total estimated
mid-year population of the state, district, or sector) and the Annual Blood Examination Rate (ABER \(= \text{total number of blood-films divided by total estimated mid-year population of the state, district, or sector}\)). Also calculated is the Slide Positivity Rate (SPR \(= \text{total positive blood-films divided by total number of blood-films collected}\)).

All other VBDCP reporting refers to 'incidence' meaning total number of new cases. In this dissertation, however, 'incidence' is used to mean new cases/population at-risk (either monthly or annual).

The annual total of Kelantan malaria cases as reported in recent VBDCP Malaysia annual reports (VBDCP Malaysia, 1993) shows a discrepancy with earlier reports, because so-called Pendalaman (Interior or Deep Jungle) Orang Asli cases were previously excluded, but are now included in the case total for Kelantan. With regard to malaria statistics, there was a demarcation between the areas administered by the Department of Orang Asli Affairs (JHEOA) and the rest of Kelantan state. Malaria cases detected (usually through PCD) in Orang Asli outside the JHEOA-administered areas were recorded as Kelantan cases, but cases detected inside JHEOA areas were unknown and unrecorded by the VBDCP. As Interior Orang Asli cases were consistently excluded from the earlier monthly and annual statistics of Kelantan, this study followed that convention.

**Geographic Variation of Incidence, Blood-film Collection, and Positive Blood-films**

Crude annual incidence in Kelantan State dropped from over 10/1000 in 1971, the first full year of the MEP Attack Phase, to less than 3/1000, and then settled into a range of 3-4/1000 during the years 1975-91, with one big drop in 1987 (Figure 1). The true population at-risk of malaria is probably less than one-half of the total state
population, since there is no malaria transmission in urban areas. The range of incidence in the 21 malaria Sectors, from 0.2/1000 to 50.6/1000 (Table 1), highlights the low risk in urban areas and the high risk in rural areas.

The Malaria-Free areas are all coastal, and growing more urbanized or suburbanized every year (District E3-Tumpat; District E7-Kota Bharu, including the state capital city of Kota Bharu; District E8-Bachok; and Sector E6b-Pasir Puteh). Being Malaria-Free areas, the only regular antimalaria measures are PCD through hospitals and clinics, and subsequent case investigation. In Malaria-Free areas, the potential vectors are An. campestris and An. sundaicus.

In Malaria-Prone areas, transmission is low or nil, but house-to-house canvassing is carried out, because vector breeding and transmission potential are believed to exist. The Malaria-Prone areas (District E5-Machang; Sector E1b-Tanah Merah; Sector E2b-Kangkong; Sector E2c-Pasir Mas; Sector E6a-Selising) also have some function as buffer zones between Malaria-Free and Malaria-Problem areas.

The Malaria-Problem areas are the two interior Districts (E4-Kuala Krai, E9-Gua Musang) and two Sectors (E1a-Air Lanas; E2a-Rantau Panjang), where the vector An. maculatus is found. Figure 4 illustrates that 50% of all Kelantan malaria cases (calendar year 1991) were detected in District E9 (comprised of three Sectors Gua Musang, Ulu Lebir, Bertam), 22% in District E1 (comprised of Sectors Air Lanas, Tanah Merah), and 15% in District E4 (comprised of Sectors Dabong, Kuala Krai, Manik Urai). The remaining 13% of cases were detected in the Malaria-Prone and Malaria-Free districts, but case investigation consistently identified those cases as imported from the Malaria-Problem districts (due to population movement).
Table 1. Kelantan Malaria Districts and Sectors, showing Populations and Crude Incidence.

<table>
<thead>
<tr>
<th>District</th>
<th>Sector</th>
<th>Code</th>
<th>1990 (est.) Pop.</th>
<th>1991 Crude Incidence (/1000)</th>
<th>Type of Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanah Merah</td>
<td>Air Lanas</td>
<td>E1a</td>
<td>36,449</td>
<td>11.6</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td></td>
<td>Tanah Merah</td>
<td>E1b</td>
<td>65,280</td>
<td>3.2</td>
<td>Mal-Prone</td>
</tr>
<tr>
<td>Pasir Mas</td>
<td>Rantau Panjang</td>
<td>E2a</td>
<td>43,896</td>
<td>1.0</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td></td>
<td>Kangkong</td>
<td>E2b</td>
<td>45,021</td>
<td>1.2</td>
<td>Mal-Prone</td>
</tr>
<tr>
<td></td>
<td>Pasir Mas</td>
<td>E2c</td>
<td>77,662</td>
<td>0.5</td>
<td>Mal-Prone</td>
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<tr>
<td>Tumpat</td>
<td>Tumpat</td>
<td>E3</td>
<td>120,468</td>
<td>0.5</td>
<td>Mal-Free</td>
</tr>
<tr>
<td>Kuala Krai</td>
<td>Dabong</td>
<td>E4a</td>
<td>17,320</td>
<td>7.8</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td></td>
<td>Kuala Krai</td>
<td>E4b</td>
<td>34,392</td>
<td>3.1</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td></td>
<td>Manik Urai</td>
<td>E4c</td>
<td>23,722</td>
<td>8.1</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td>Machang</td>
<td>Machang</td>
<td>E5</td>
<td>83,539</td>
<td>0.6</td>
<td>Mal-Prone</td>
</tr>
<tr>
<td>Pasir Puteh</td>
<td>Selising</td>
<td>E6a</td>
<td>56,777</td>
<td>0.4</td>
<td>Mal-Prone</td>
</tr>
<tr>
<td></td>
<td>Pasir Puteh</td>
<td>E6b</td>
<td>61,870</td>
<td>0.2</td>
<td>Mal-Free</td>
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<tr>
<td>Kota Bharu</td>
<td>Keterah</td>
<td>E7a</td>
<td>347,762</td>
<td>0.3</td>
<td>Mal-Free</td>
</tr>
<tr>
<td></td>
<td>Wakaf Che Yeh</td>
<td>E7b</td>
<td></td>
<td></td>
<td>Mal-Free</td>
</tr>
<tr>
<td></td>
<td>Kubang Kerian</td>
<td>E7c</td>
<td></td>
<td></td>
<td>Mal-Free</td>
</tr>
<tr>
<td></td>
<td>Pangkalan Chepa</td>
<td>E7d</td>
<td></td>
<td></td>
<td>Mal-Free</td>
</tr>
<tr>
<td>Bachok</td>
<td>Bachok</td>
<td>E8</td>
<td>102,491</td>
<td>0.2</td>
<td>Mal-Free</td>
</tr>
<tr>
<td>Gua Musang</td>
<td>Gua Musang</td>
<td>E9a</td>
<td>27,436</td>
<td>8.1</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td></td>
<td>Ulu Lebir</td>
<td>E9b</td>
<td>19,013</td>
<td>50.6</td>
<td>Mal-Problem</td>
</tr>
<tr>
<td></td>
<td>Bertam</td>
<td>E9c</td>
<td>6,598</td>
<td>39.0</td>
<td>Mal-Problem</td>
</tr>
</tbody>
</table>


Figure 4 also shows the distribution of cases stratified by collection source (PCD/ACD/INV). The largest number of cases are detected by PCD (hospitals and clinics) which are located in all districts and sectors. The majority of cases are detected in the Malaria-Problem districts, while the majority of the cases detected in Malaria-
Free districts get classified as imported from other Malaria-Problem districts. ACD (house-to-house surveillance) does not occur in Malaria-Free districts. The bulk of INV cases are detected in mass blood surveys in three Malaria-Problem districts.

In short, the rural and interior districts have smaller populations and high incidence, while the coastal and urban districts have little malaria (which is imported through population movement, not transmission).

Operational Malaria Data

A monthly summary of malaria cases (persons with positive blood-films) is routinely compiled by VBDCP staff throughout Malaysia. These operational data were used for analysis, over the time period January 1980-December 1991, for Kelantan state.

The monthly summary of positive blood-films is stratified at state-, district-, and sector-level according to source of blood-film (ACD/PCD/INV), male/female distribution of cases, parasite species, age-groups, and investigation classification. This work is done as separate, independent tabulations, but cross-tabulations (e.g., age- and sex-specific cross-tab; or species- and source-specific cross-tabulations) are not done, due to lack of computerized databases. The monthly summary of all blood-films examined is stratified only according to source of blood-film, thus no denominator exists for other stratifications (e.g., age, sex).

Blood-film reporting can be delayed, i.e. a blood-film collected in late January may have the result recorded in February. Each month's reporting is 'closed' on a certain date, after which any further reported cases are counted in the next month.
This late reporting is a regular element of the system, and the net effect is that peaks of transmission can be partly shifted to the succeeding month.

**Entomological Data**

Entomological studies in Malaysia have faced a chronic problem with the low numbers of vectors encountered in the field (Chooi, 1985). This is a longstanding problem in Kelantan, where entomological surveillance of *An. maculatus* yields exceedingly sparse data. Any association between rainfall and malaria necessarily acts through the intermediate role of vector breeding and density, but entomological surveillance records in Kelantan showed very low vector densities, in spite of continued malaria transmission.

**METEOROLOGICAL DATA**

Recent meteorological data are available from dozens of stations in Kelantan under the auspices of the Departments of Meteorology, Drainage and Irrigation, Agriculture, University Science Malaysia, and some agricultural plantations, but only a handful of stations are located in Malaria-Problem areas and of these, only six were found with data extending back continuously to 1980 (Orang Asli Betis, Bertam Baru, Jeli, Gua Musang, Bertam Baru, Dabong). Only one rainfall station has data extending back to 1970 (Kota Bharu airport).

Of the six interior stations, the variance between and among months was high, and each station's dataset had one or two gaps (no data). Therefore, an arithmetic mean of those six rainfall stations sited in the interior Malaria-Problem areas was used: Jeli (E1a), Dabong (E4a), Gua Musang (E9a), Aring (E9b), Bertam (E9c), Betis (E9c).
These six represented good geographic coverage of the important malaria transmission areas, all six had nearly continuous monthly data from January 1980 to present, and data gaps were non-overlapping. Rainfall stations from Malaria-Free and Malaria-Prone sectors were not appropriate due to lack of transmission in those areas.

EL NIÑO SOUTHERN OSCILLATION

Annual number of malaria cases detected in Peninsular Malaysia, Sabah State, and Kelantan State were collected from several sources (VBDCP Kelantan, 1983; VBDCP Kelantan 1991a; VBDCP Malaysia, 1993; Mak et al., 1992) in order to present the longest possible time series. Total malaria in Malaysia was not presented, because during the period 1961-1975, Peninsular Malaysia malaria heavily weighted the national total, and from 1975-1992, Sabah malaria heavily weighted the national total.

Rainfall data from one Kelantan coastal station, Kota Bharu airport, were obtained extending back to January 1970, and from one interior station, Orang Asli Betis, which began recording in January 1974 (Department of Meteorology Malaysia, 1970-91).

MOVING AVERAGES (TIME-SERIES ANALYSIS)

Three-month moving averages were used to model the malaria and rainfall time series data. Three-month moving average has the effect of reducing the amplitude of the peaks and valleys and smoothing out single-month quirks in the data.

Late reporting of malaria cases is one such quirk that can shift one month's cases into the next month, mainly due to processing constraints (e.g., backlog of blood-
films during high transmission season), logistical problems (e.g., flooding), and other work interruptions (e.g., the fasting month of Ramadan). Therefore, to smooth the malaria case data, it was believed logical to use the three-month mean of previous month + current month + next month.

Monthly rainfall is used as an indicator of adequate and suitable vector breeding sites (seepages and small, slow-moving streams). As with malaria cases, it was believed logical (and proved empirically useful) to use the three-month mean of previous month + current month + next month.

Graphing of the moving averages of malaria and rainfall were presented without a shift or adjustment for the time-lag between occurrence of rainfall and later effect on occurrence of malaria. However, consideration of the mosquito’s gonotrophic cycle (2-4 days) and developmental cycle (1-2 weeks), and the incubation period of the parasite in the mosquito (1-2 weeks) and in humans (2 weeks) suggests 1-2 months as the appropriate lag to be visualized between rainfall and the effect of rainfall through vector density on malaria incidence.

A nonparametric sign test was used to assess the association of rainfall to malaria. Rainfall and change in malaria incidence were each scored on a dichotomous scale (1 or 0). The monthly change in malaria incidence was scored:

1 = incidence increased from previous month
0 = incidence decreased from previous month

The monthly rainfall was scored:

1 = rainfall greater than 100 mm and less than 200 mm
0 = rainfall less than 100 mm or greater than 200 mm
Each monthly malaria score was paired with previous month’s rainfall score (one-month lag), and pairing of each rainfall score with next month’s malaria score produced a 2x2 table and a chi-square statistic with 1 d.f.

**GUA MUSANG AGE- AND SEX-SPECIFIC INCIDENCE RATES**

The 1991 blood-film collection of Gua Musang district was entered to a computerized database from the laboratory logbooks and other record files. The entire dataset was sorted, reviewed, and censored for duplicate positive blood-films (follow-up blood-films from the same case). The previously described operational rules defining a recrudescence (1 month) and a relapse (6 months) were used. Repeat negative blood-films in the same individual were not censored (because each blood-film represents suspicion of possible malaria infection, and because names of negatives were not entered to the database).

**Passive Case Detection (PCD)**

All 1991 PCD blood-film results from Gua Musang Hospital laboratory were entered to the database file. Ten duplicate blood-films (based on name and age) were censored from the PCD dataset:

- 3 Pf cases had repeat blood-film positive on day 1 or day 2
- 1 Pf case had repeat blood-film positive on day 4
- 2 Pf cases had repeat blood-film positive on day 6
- 1 Pf case had repeat blood-film positive on day 18
- 1 case Pv-positive, then Pf-positive on day 101, then Pf-positive on day 25, then Pf-positive on day 31, then Pf-positive on day 53 (this series was counted as 1 Pv case and 1 Pf case)

Not censored:
- 2 Pf cases had second blood-film positive on day 59 or day 112
Active Case Detection (ACD)

All available 1991 ACD blood-film results from Gua Musang record files were entered to the database file. Four duplicate blood-films were censored from the ACD dataset:

1 Pf case had repeat blood-film positive on day 27
3 Pv cases had repeat blood-film positive on day 29, day 34, or day 71

Not censored:
5 Pf cases later Pf-positive at day 33 to day 95
3 Pv cases later Pf-positive at day 32 to day 118
1 Pf case later Pv-positive at day 43

Mass Blood Survey/Investigational Detection (INV)

All available 1991 INV blood-film results from Gua Musang record files were entered to the database file. Only one duplicate name was found in the INV dataset, which was Pv, then Pf on day 65, and was counted as two cases.

Census Age- and Sex-Structure

Preliminary data from the 1991 National Census were available for total Gua Musang population, male:female population, and rural:urban population, but no age-stratified population data are yet available from the 1991 census.

The age-structure of Gua Musang (as the old name, Ulu Kelantan) was available from the 1980 National Census, but cross-tabulated age- and sex-stratified census data was unavailable for districts.

Data Analysis

Epi Info software was used for data entry, frequency calculations, and cross-tabulations.
CASE-CONTROL PROTOCOL FOR PERSONAL AND BEHAVIORAL RISK FACTORS ASSOCIATED WITH MALARIA INFECTION

The case-control study was conducted in Kampung Jerek, Sector Bertam Baru (E9c), Kelantan (one of the most malarious villages in Kelantan for many years). The village was a site of a bednet trial during 1987-89. Periodic ACD by house-to-house canvassers is carried out in this village.

The survey questionnaire was designed to examine hypothesized risk factors for malaria infection, including determinants commonly found on the case-investigation form used for malaria surveillance. These conventional determinants included: recent travel, type of house, use of bednet or prophylaxis, nearby vector breeding.

The sampling frame was defined by all those individuals in the Kampung Jerek area who were blood-filmed by ACD during 1991 (an area of interest to the VBDCP due to high recorded incidence of malaria in previous years).

ACD canvassers had gone house-to-house in January/May/June/July of 1991 and January 1992, taking blood-films from anyone with fever, or history of recent fever. These blood-films were subsequently routinely examined by a trained VBDCP malaria microscopist. Thus the blood-films were taken from suspected malaria cases, and the subsequent unbiased examination (either positive or negative for malaria parasites) determined their status as a case or non-case in the study.

A case was defined as someone who was blood-film positive in the course of one of the ACD surveys of 1991. The definition of a matched control was a person of the same age-group as the case, who was blood-film negative in the same ACD survey.
Matching followed these rules:

1. Both case and non-case subjects were blood-filmed in the same village during the same blood survey (the surveys were completed in 3-5 days).

2. Age-matching by age-groups:
   0-11 months, 1-4 years, 5-9 years, 10-14 years, 15-19 years, 20-29 years, 30-39 years, 40 years or older

3. Case and non-case from same village, but different house.

   With the assistance of knowledgeable malaria staff, it was possible to trace blood-film-positive persons and matched non-cases. The survey instrument was administered in Malay language. When matched pairs were children, a parent was interviewed. Repeated attempts were made to follow-up both case and non-case.

   Epi Info software was used for bivariate analysis of the data.
CHAPTER 4: RESULTS

The results of this study are organized at three different levels of observation: the state (malaria in relation to inter-annual ENSO and intra-annual rainfall), district (age- and sex-specific risk groups relative to blood-film collection method), and village (environmental and behavioral determinants of malaria).

EL NIÑO SOUTHERN OSCILLATION AND MALARIA OCCURRENCE

In Peninsular Malaysia, Kelantan State, and Sabah (the east Malaysian state with high malaria occurrence), each appears to show an association between El Niño Southern Oscillation (ENSO) events and detection of fewer malaria cases (Figure 5). The association is not absolute, e.g., during 1969-70 and 1976-77 there is no decrease of malaria in Sabah and Kelantan, and it is noteworthy that some ENSOs occurred during long periods of decreasing malaria cases detected, e.g. Sabah during 1961-69, and Peninsular Malaysia during 1971-81. Nonetheless, detected malaria cases decreased or remained the same during all ENSOs (with one exception, 1969-70 in Sabah), and all increases of malaria cases detected occurred between ENSOs. Considering the last eight ENSOs (1963-64, 1965-66, 1969-70, 1972-73, 1976-77, 1982-83, 1986-87, 1991-93), annual malaria cases detected decreased in Peninsular Malaysia in association with eight ENSOs, and in Sabah, annual malaria cases detected decreased during seven ENSOs. In Kelantan, annual malaria cases detected decreased during four of the last five ENSOs.
Kota Bharu (coastal) monthly rainfall (Figure 6) was not dramatically different during recent ENSOs (1972-73, 1976-77, 1982-83, 1986-87). Nonetheless, dry periods during ENSO events were usually of longer duration (4-6 months) than during non-ENSO years (2-4 months), but long dry periods occurred in some non-ENSO years (1974, 1989). The annual spike of high rainfall in November-December was reduced in 1972, but not during the other ENSO periods.

Betis (interior) monthly rainfall data (Figure 7) only span three ENSO events (1976-77, 1982-83, 1986-87). ENSO-associated dry periods were 4 months (January-April 1977, January-April 1987) or 6 months (January-June 1983), while non-ENSO years had shorter dry periods of 2-3 months.

CORRELATION OF BLOOD-FILMS COLLECTED (PCD/ACD/INV) AND MALARIA CASES DETECTED

In operational data of the VBDCP Kelantan, the monthly variation in malaria cases detected was not obviously associated with variation in blood-film collection. Blood-films collected and malaria cases detected by PCD were not correlated ($r = -0.0141$, $p > 0.01$, Table 2), however, the number of PCD cases was highly correlated with PCD Slide Positivity Rate (SPR, the ratio of positive blood-films divided by total blood-films) ($r=0.7599$, $p < 0.001$, Table 2). Similarly, blood-films collected were not correlated with malaria cases detected by ACD ($r=0.0620$, $p > 0.01$, Table 2), whereas the number of ACD cases was highly correlated with ACD SPR ($r=0.8118$, $p < 0.001$, Table 2).

INV cases were correlated with INV blood-films collected ($r=0.4578$, $p < 0.001$, Table 2), but monthly INV cases also correlate with INV SPR ($r=0.7142$, $p < 0.001$, Table 2).
Table 2. Correlations of monthly total blood-films collected (by PCD, ACD, and INV), total malaria cases detected (positive blood-films), and slide positivity rate (SPR), Kelantan state, 1980-90.

<table>
<thead>
<tr>
<th>Correlations:</th>
<th>PCD-case</th>
<th>PCD-BFs</th>
<th>ACD-case</th>
<th>ACD-BFs</th>
<th>INV-case</th>
<th>INV-BFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCD-case</td>
<td>1.0000</td>
<td>-0.0141</td>
<td>0.3688**</td>
<td>-0.1124</td>
<td>0.4250**</td>
<td>0.3196**</td>
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<tr>
<td>PCD-BFs</td>
<td>-0.0141</td>
<td>1.0000</td>
<td>0.4475**</td>
<td>-0.0707</td>
<td>0.0132</td>
<td>0.0161</td>
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<tr>
<td>ACD-case</td>
<td>0.3688**</td>
<td>0.4475**</td>
<td>1.0000</td>
<td>0.0620</td>
<td>0.2184</td>
<td>0.0183</td>
</tr>
<tr>
<td>ACD-BFs</td>
<td>-0.1124</td>
<td>-0.0707</td>
<td>0.0620</td>
<td>1.0000</td>
<td>-0.1258</td>
<td>0.1774</td>
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<tr>
<td>INV-case</td>
<td>0.4250**</td>
<td>0.0132</td>
<td>0.2184</td>
<td>-0.1258</td>
<td>1.0000</td>
<td>0.4578**</td>
</tr>
<tr>
<td>INV-BFs</td>
<td>0.3196**</td>
<td>0.0161</td>
<td>0.0183</td>
<td>0.1774</td>
<td>0.4578**</td>
<td>1.0000</td>
</tr>
<tr>
<td>All-case</td>
<td>0.8675**</td>
<td>0.1248</td>
<td>0.5926**</td>
<td>-0.1029</td>
<td>0.7508**</td>
<td>0.3922**</td>
</tr>
<tr>
<td>All-BFs</td>
<td>0.1111</td>
<td>0.7645**</td>
<td>0.3785**</td>
<td>0.3637**</td>
<td>0.1968</td>
<td>0.5694**</td>
</tr>
<tr>
<td>SPR-PCD</td>
<td>0.7599**</td>
<td>-0.6245**</td>
<td>-0.0277</td>
<td>0.0307</td>
<td>0.2853**</td>
<td>0.2345*</td>
</tr>
<tr>
<td>SPR-ACD</td>
<td>0.3340**</td>
<td>0.4283**</td>
<td>0.8118**</td>
<td>-0.4507**</td>
<td>0.2038</td>
<td>-0.1497</td>
</tr>
<tr>
<td>SPR-INN</td>
<td>0.1881</td>
<td>0.0196</td>
<td>0.2155</td>
<td>-0.2812*</td>
<td>0.7142**</td>
<td>-0.1553</td>
</tr>
<tr>
<td>SPR-all</td>
<td>0.8205**</td>
<td>-0.2720*</td>
<td>0.3991**</td>
<td>-0.2281*</td>
<td>0.6367**</td>
<td>0.1174</td>
</tr>
</tbody>
</table>

No. of months: 132  two-tailed Significance: * = p < 0.01  ** = p < 0.001

<table>
<thead>
<tr>
<th>Correlations:</th>
<th>All-case</th>
<th>All-BFs</th>
<th>SPR-PCD</th>
<th>SPR-ACD</th>
<th>SPR-INN</th>
<th>SPR-all</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCD-case</td>
<td>0.8675**</td>
<td>0.1111</td>
<td>0.7599**</td>
<td>0.3340**</td>
<td>0.1881</td>
<td>0.8205**</td>
</tr>
<tr>
<td>PCD-BFs</td>
<td>0.1248</td>
<td>0.7645**</td>
<td>-0.6245**</td>
<td>0.4283**</td>
<td>0.0196</td>
<td>-0.2720*</td>
</tr>
<tr>
<td>ACD-case</td>
<td>0.5926**</td>
<td>0.3785**</td>
<td>-0.0277</td>
<td>0.8118**</td>
<td>0.2155</td>
<td>0.3991**</td>
</tr>
<tr>
<td>ACD-BFs</td>
<td>-0.1029</td>
<td>0.3637**</td>
<td>0.0307</td>
<td>-0.4507**</td>
<td>-0.2812*</td>
<td>-0.2281*</td>
</tr>
<tr>
<td>INV-case</td>
<td>0.7508**</td>
<td>0.1968</td>
<td>0.2853**</td>
<td>0.2038</td>
<td>0.7142**</td>
<td>0.6367**</td>
</tr>
<tr>
<td>INV-BFs</td>
<td>0.3922**</td>
<td>0.5694**</td>
<td>0.2345*</td>
<td>-0.1497</td>
<td>-0.1553</td>
<td>0.1174</td>
</tr>
<tr>
<td>All-case</td>
<td>1.0000</td>
<td>0.2587*</td>
<td>0.5551**</td>
<td>0.5128**</td>
<td>0.4869**</td>
<td>0.8673**</td>
</tr>
<tr>
<td>All-BFs</td>
<td>0.2587*</td>
<td>1.0000</td>
<td>-0.3601*</td>
<td>0.1105</td>
<td>-0.1550</td>
<td>-0.2290*</td>
</tr>
<tr>
<td>SPR-PCD</td>
<td>0.5551**</td>
<td>-0.3601**</td>
<td>1.0000</td>
<td>-0.0740</td>
<td>0.1082</td>
<td>0.7736**</td>
</tr>
<tr>
<td>SPR-ACD</td>
<td>0.5128**</td>
<td>0.1105</td>
<td>-0.0740</td>
<td>1.0000</td>
<td>0.3327**</td>
<td>0.4278**</td>
</tr>
<tr>
<td>SPR-INN</td>
<td>0.4869**</td>
<td>-0.1550</td>
<td>0.1082</td>
<td>0.3327**</td>
<td>1.0000</td>
<td>0.5632**</td>
</tr>
<tr>
<td>SPR-all</td>
<td>0.8673**</td>
<td>-0.2290*</td>
<td>0.7736**</td>
<td>0.4278**</td>
<td>0.5632**</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

No. of months: 132  two-tailed Significance: * = p < 0.01  ** = p < 0.001

Source: VBDCP Kelantan.
There were no obvious correlations between the monthly blood-films collected by PCD, ACD, and INV, however, monthly malaria cases detected by PCD and ACD ($r=0.3688$, $p<0.001$, Table 2) or by PCD and INV ($r=0.4250$, $p<0.001$, Table 2) were significantly correlated. PCD cases were positively correlated with INV blood-film collection ($r=0.3196$, $p<0.001$, Table 2).

SEASONALITY OF RAINFALL AND MALARIA

Coastal Kelantan rainfall (represented by Kota Bharu airport, Figure 6), exhibited a consistent annual pattern, with extremely high rainfall (> 500 mm) in either November or December, resulting in flooding, followed by 3-6 months of extremely low rainfall (< 100 mm), followed by 5-7 months of moderate rainfall culminating in the next flood. Interior Kelantan rainfall (represented by Orang Asli Betis station, Figure 7) was generally more moderate than at the coast, being lower in November-December, and higher in mid-year.

Despite variation in rainfall between and among rainfall stations, there were significant correlations between all six rainfall stations in the interior and rainfall at Kota Bharu on the coast (Table 3).

The three-month moving average of mean rainfall of the six interior rainfall stations ('composite rainfall') showed two annual peaks of rainfall centered on April-May and September-November (Figure 9).

During 10 of 12 years (1980-91), the three-month moving average of PCD + ACD malaria cases exhibited a peak centered on June-July; in four of 12 years, there was a peak centered on November-December (Figure 9).
Table 3. Correlations of monthly rainfall from seven stations, Kelantan, 1980-91

<table>
<thead>
<tr>
<th>Correlations:</th>
<th>Aring</th>
<th>Bertam</th>
<th>Betis</th>
<th>Dabong</th>
<th>Gua Musang</th>
<th>Jeli</th>
<th>Kota Bharu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aring</td>
<td>1.0000</td>
<td>0.4144**</td>
<td>0.4708**</td>
<td>0.4288**</td>
<td>0.5324**</td>
<td>0.7853**</td>
<td>0.5626**</td>
</tr>
<tr>
<td>Bertam</td>
<td>0.4144**</td>
<td>1.0000</td>
<td>0.3889**</td>
<td>0.5800**</td>
<td>0.3577**</td>
<td>0.3402**</td>
<td>0.2264*</td>
</tr>
<tr>
<td>Betis</td>
<td>0.4708**</td>
<td>0.3889**</td>
<td>1.0000</td>
<td>0.3920**</td>
<td>0.5251**</td>
<td>0.4532**</td>
<td>0.2631*</td>
</tr>
<tr>
<td>Dabong</td>
<td>0.4288**</td>
<td>0.5800**</td>
<td>0.3920**</td>
<td>1.0000</td>
<td>0.3660**</td>
<td>0.5635**</td>
<td>0.4364**</td>
</tr>
<tr>
<td>Gua Musang</td>
<td>0.5324**</td>
<td>0.3577**</td>
<td>0.5251**</td>
<td>0.3660**</td>
<td>1.0000</td>
<td>0.5511**</td>
<td>0.2836**</td>
</tr>
<tr>
<td>Jeli</td>
<td>0.7853**</td>
<td>0.3402**</td>
<td>0.4532**</td>
<td>0.5635**</td>
<td>0.5511**</td>
<td>1.0000</td>
<td>0.6202**</td>
</tr>
<tr>
<td>Kota Bharu</td>
<td>0.5626**</td>
<td>0.2264*</td>
<td>0.2631*</td>
<td>0.4364**</td>
<td>0.2836**</td>
<td>0.6202**</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

No. of months: 144  two-tailed Significance: * = p < 0.01  ** = p < 0.001

Sources: Department of Meteorology Malaysia, 1970-91; Department of Drainage and Irrigation Kelantan, 1984-91.

Association of Rainfall and Kelantan State Malaria

From 1980-91, malaria incidence declined seven of eight times when composite monthly rainfall was less than 100 mm (Figure 9). From 1980-91, malaria incidence also declined 10 of 13 times when composite monthly rainfall was greater than 200 mm (Figure 9). During three periods, August 1982, February-August 1984, and July 86, malaria decreased in spite of monthly rainfall less than 200 mm.

A nonparametric sign test showed the association between moderate rainfall (greater than 100 mm and less than 200 mm) with increase in next month's malaria, and high or low rainfall (greater than 200 mm or less than 100 mm) with decrease of next month's malaria was significant (chi-square=11.87, p=0.0006, Table 4).

<table>
<thead>
<tr>
<th>Monthly Rainfall (three-month moving average)</th>
<th>Monthly Malaria Incidence (three-month moving average)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased (from previous month)</td>
</tr>
<tr>
<td>&gt; 100 mm and &lt;200 mm</td>
<td>37</td>
</tr>
<tr>
<td>&lt; 100 mm or &gt;200 mm</td>
<td>25</td>
</tr>
</tbody>
</table>

Chi-square = 11.87, p = 0.0006

OTHER SEASONAL DETERMINANTS OF MALARIA OCCURRENCE

Fruit Production and Malaria

Ponnampalam (1975) reported that the durian fruit season was associated with higher malaria incidence (in an area on the west coast, not Kelantan). Health and medical staff believe this hypothesis to be true in Kelantan (personal communication), and annual reports have mentioned it (VBDCP Kelantan, 1983-88). The hypothesis has three elements:

- more people venture into the forest to collect the valuable durian fruit, and even to sleep beneath and thereby guard the trees;
- more people are out at night markets shopping for fruit;
- the population is reluctant to consume anti-malaria drugs in combination with durian fruit (believed to be a dangerous mixture).

The VBDCP annual reports of 1983-88 list June-August as the durian season, while July-September was offered by some informants (Ponnampalam reported early
June to mid-September), but it was not possible to document the dates of past fruit seasons with certainty. Interviews with fruit farmers indicated that fruit seasons vary from year to year, locality to locality, and even tree to tree.

Kelantan incidence data (Figure 9) suggested that a peak of malaria centered on either June, July, or August, has occurred in most years (but not 1980, 1984, 1985), however, those peaks start building 2-3 months prior to the beginning of the fruit season.

It is plausible that the durian effect is acting to increase transmission, on top of transmission already rising due to rainfall. This intriguing and plausible hypothesis could not be confirmed nor excluded. Rainfall data seems to provide explanation for the observed tops and bottoms of malaria, but durian-related transmission remains as an unresolved confounding factor.

Rubber Production

Rubber-tapping is a major economic activity in Kelantan. It is primarily a small-holder system, whereby many residents own modest acreage. They tap the trees themselves, and may also hire workers to assist in the work. Many of the hired workers are economic migrants from neighboring countries.

There are two kinds of major fluctuations in rubber production: the intra-annual "fall" season centered on March-April, when the rubber trees drop their leaves, enter a period of hibernation, and are left untapped; and less-predictable inter-annual periods of higher or lower price-demand for rubber output which might influence malaria incidence, both by attracting more economic migrants who might import malaria, and
by placing more susceptibles in the forest transmission environment. A rubber price rally occurred in 1988, which coincides with malaria increasing from 1987 to 1988.

Rubber production (Peninsular Malaysia, 1986-91, Figure 10) was low in April of each year, with two annual peaks in July and December-January. The first peak coincides with a malaria peak, but the second does not. Thus, an association between rubber and malaria transmission is suggestive, but could neither be confirmed nor excluded. Rubber-related transmission is an unresolved possible confounding factor.

AGE- AND SEX-SPECIFIC RISK GROUPS IN RELATION TO PCD, ACD, AND INV BLOOD-FILM COLLECTION

The total population of Gua Musang district in the 1991 national census was 63,865 (urban = 14,465 and rural = 49,400; Department of Statistics Malaysia, 1991). The Gua Musang rural male:female ratio was 1.22:1, whereas in Kelantan state as a whole, the rural male:female ratio was 0.97:1. This great discrepancy reflects the fact that Gua Musang attracts large numbers of single males to work in timber and plantations. Fully 7178 (61%) of the 11,766 blood-films collected were from males (Table 5). There were 11,766 total blood-films (ACD, PCD, and INV) in the Gua Musang dataset of calendar year 1991, of which 541 were malaria-positive.

Table 5. Sex distribution of persons blood-filmed in Gua Musang District, 1991.

<table>
<thead>
<tr>
<th>Sex</th>
<th>No.BF</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4588</td>
<td>39.0%</td>
</tr>
<tr>
<td>Male</td>
<td>7178</td>
<td>61.0%</td>
</tr>
<tr>
<td>Total</td>
<td>11766</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
The age distribution of the blood-film dataset was bimodal on ages 5-9 years and 20-24 years (Table 6). This matched the bimodal distribution of the district census population, but did not match the State census population (Figure 11).

Table 6. Age distribution of persons blood-filmed in Gua Musang District, 1991.

<table>
<thead>
<tr>
<th>Age-group</th>
<th>No.BF</th>
<th>Percent</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 mon</td>
<td>318</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>1-4 yr</td>
<td>1572</td>
<td>13.4%</td>
<td>16.1%</td>
</tr>
<tr>
<td>5-9 yr</td>
<td>1775</td>
<td>15.1%</td>
<td>31.1%</td>
</tr>
<tr>
<td>10-14 yr</td>
<td>1359</td>
<td>11.6%</td>
<td>42.7%</td>
</tr>
<tr>
<td>15-19 yr</td>
<td>1226</td>
<td>10.4%</td>
<td>53.1%</td>
</tr>
<tr>
<td>20-24 yr</td>
<td>1496</td>
<td>12.7%</td>
<td>65.8%</td>
</tr>
<tr>
<td>25-29 yr</td>
<td>1182</td>
<td>10.0%</td>
<td>75.9%</td>
</tr>
<tr>
<td>30-34 yr</td>
<td>920</td>
<td>7.8%</td>
<td>83.7%</td>
</tr>
<tr>
<td>35-39 yr</td>
<td>651</td>
<td>5.5%</td>
<td>89.2%</td>
</tr>
<tr>
<td>40-44 yr</td>
<td>460</td>
<td>3.9%</td>
<td>93.1%</td>
</tr>
<tr>
<td>45-49 yr</td>
<td>299</td>
<td>2.5%</td>
<td>95.7%</td>
</tr>
<tr>
<td>50-54 yr</td>
<td>228</td>
<td>1.9%</td>
<td>97.6%</td>
</tr>
<tr>
<td>55-59 yr</td>
<td>101</td>
<td>0.9%</td>
<td>98.5%</td>
</tr>
<tr>
<td>60+ yr</td>
<td>162</td>
<td>1.4%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Age Unknown</td>
<td>17</td>
<td>0.1%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>11766</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Total blood-films collected and malaria cases detected, by collection source, Gua Musang District, 1991.

<table>
<thead>
<tr>
<th>Detection Method</th>
<th>No. of Blood-films</th>
<th>No. of Positive Blood-films</th>
<th>Blood-film Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>6422 (54.6%)</td>
<td>258 (47.7%)</td>
<td>4.0%</td>
</tr>
<tr>
<td>INV</td>
<td>3221 (27.4%)</td>
<td>128 (23.7%)</td>
<td>4.0%</td>
</tr>
<tr>
<td>PCD</td>
<td>2123 (18.0%)</td>
<td>155 (28.7%)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Total</td>
<td>11766 (100.0%)</td>
<td>541 (100.0%)</td>
<td>4.6%</td>
</tr>
</tbody>
</table>
More blood-films were collected by ACD (54.6%) than INV and PCD (Table 7). Similarly, more malaria cases were detected by ACD (47.7%) than INV and PCD (Table 7). By contrast, PCD had a higher positivity rate (7.3%) than either ACD or INV (Table 7).

Age- and sex-specific census population data at district level were not available. Therefore age-specific population data from the 1980 district census (Department of Statistics Malaysia, 1983) were consulted. The age structure of the 1980 district census population was similar to the age structure of the blood-film collection, in contrast to the total State census population which differed greatly: the district census population and the blood-film collection were bimodal (at age groups 5-9 years and 20-24 years), and had an excess of persons in the age groups 15-39 years (relative to the state census population), and a dip in the age groups over 50 years (Figure 11).

To describe and evaluate risk groups for malaria, and to describe the completeness of coverage of the blood-film collection, two different age-specific incidence rates were calculated from these blood-film data: the incidence of having a blood-film obtained, and the incidence of having malaria (Figure 12). The denominator used was calculated by indirect standardization applying the 1980 district census age-structure to the 1991 total district population.

The rate of blood-film collection in Gua Musang during 1991 was 184 blood-films/1000 population (11,766 blood-films/63,865 population). Relative to this overall rate of blood-film collection, age groups 10-29 years old appear to have been oversampled, while age groups over 35 years appear to have been undersampled (Figure 12).
Age-specific incidence rate was bimodal on age-group 1-4 years and age-groups 15-29 years (Figure 12).

The age- and sex-specific distribution of the blood-film collection was used as a substitute denominator for the unavailable district census population. The age structures of the district population and the blood-film collection were similar (Figure 11), the age-specific incidence of malaria cases per 1000 population and of malaria cases per 1000 blood-films were also similar (Figure 13). Furthermore, the male:female ratio in the blood-film collection (1.56:1) was similar to the male:female ratio in the district census data (1.22:1), in being skewed toward males.

The age structure of male and female blood-film collections differed greatly by the three collection methods (Figures 14, 15, and 16). In general, both male and female blood-film collections were highest in young children by all three collection methods, but only in males was there a peak in blood-film collection frequency in young adults age 20-24 years by ACD (Figure 15), and by INV (Figure 16), or in persons age 25-29 by PCD (Figure 14).

The high frequency of blood-film collection in children 1-4 years old by PCD reflects intentional oversampling at antenatal and toddler clinic visits. Similarly, children 5-9 years old are oversampled by INV in school surveys.

Falciparum and vivax incidence figures (Figure 13) were heavily weighted by higher male incidence rates, as can be seen by comparing age-specific incidence figures by gender (Figure 17).

Age-specific incidence rates of malaria (falciparum and vivax combined) in males in the age groups 0-34 years were highest by PCD blood-film collection
(Figure 18). Similarly, age-specific incidence rates in females in age groups 0-39 years were also higher by PCD blood-film collection (Figure 19).

Age-specific incidence rates of malaria in males 35 years and older was highest by INV blood-film collection (Figure 18).

Age-specific *P. falciparum* gametocytemia was generally low in males (<30/1000, Figure 20) and even lower in females (<22/1000, Figure 21).

Nonetheless, in comparing the three blood-film collection methods, age-specific incidence of gametocytemia in males was highest as detected by ACD and INV blood-film collection, while gametocytemia rates as detected by PCD were zero in most male age groups (Figure 20). In females, age-specific gametocytemia showed mixed results: the highest incidence by ACD blood-film collection was in young girls ages 1-9 years old and older women ages 45-49 years old, and the highest incidence by PCD blood-film collection was in adult women ages 25-29 years old and 35-39 years old (Figure 21).

**CASE-CONTROL SUBSTUDY OF PERSONAL AND ENVIRONMENTAL RISK FACTORS FOR MALARIA INFECTION IN KAMPUNG JEREK, 1991-92**

The 1991 Case Register Book of Bertam Baru Sector listed 85 cases in Kampung Jerek occurring in 74 different people. Sixteen of the 74 malaria-positive people during 1991 were matched and enrolled in the study, and an additional six matched pairs were enrolled during January 1992, making a total of 22 (Table 8). Substantial loss of available cases was due in part to high mobility, e.g., 14 malaria-positive persons could not be interviewed due to their return to Thailand after temporary residence in Kampung Jerek during 1991. (These people were reported to
be Malay people of Thai nationality, mostly relatives who came to Kampung Jerek for temporary employment or social visits.)

Bivariate statistical analysis showed no significant differences between cases and non-cases in any of the parameters examined (Appendix C), although the small sample size may have prevented detection of risk factors.

Table 8. Disposition of 74 Malaria-Positive Cases During Follow-up Interview in Kampung Jerek Case-Control Study, January-February 1992.

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCD case-excluded from study&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>16.2%</td>
</tr>
<tr>
<td>ACD form missing-matching impossible&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
<td>10.8%</td>
</tr>
<tr>
<td>Age-matched non-case unavailable</td>
<td>3</td>
<td>4.1%</td>
</tr>
<tr>
<td><strong>Unavailable for interview:</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Returned to Thailand</td>
<td>14</td>
<td>18.9%</td>
</tr>
<tr>
<td>Not home/unable to contact</td>
<td>13</td>
<td>17.6%</td>
</tr>
<tr>
<td>Untraceable/unknown person</td>
<td>7</td>
<td>9.5%</td>
</tr>
<tr>
<td>Deceased</td>
<td>1</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Case and matched non-case interviewed</strong></td>
<td>16</td>
<td>21.6%</td>
</tr>
</tbody>
</table>

<sup>a</sup> PCD cases were excluded from the study, because PCD is not comparable to ACD/INV house-to-house blood-film collection, and because of the difficulties of tracing a PCD case and a matching non-case.

<sup>b</sup> The original blood-film register forms were missing for one month’s ACD survey, consequently it was impossible to match any non-cases for the 8 cases. For a further 3 cases, although the blood-film register form was available, no age-matched non-case could be found.

<sup>c</sup> Nearly half (35/74) of the recorded malaria-positive people were unavailable for interview because they were returned to Thailand, not at home, unknown at the recorded address, or deceased.
CHAPTER 5: DISCUSSION

EL NIÑO SOUTHERN OSCILLATION

The observation of lower occurrence of malaria cases associated with recent El Niño Southern Oscillation (ENSO) events (Figure 5) contrasts with recent articles that have linked ENSO-related flooding to epidemics of malaria and other vector-borne disease elsewhere in the world. Nicholls (1993) noted major epidemics of malaria in 1983, in Ecuador, Peru, and Bolivia after heavy rain and flooding. Bouma et al. (1993) extend this observation to several other regions of the world. Loevinsohn (1994) specifically linked rising temperature with an epidemic outbreak of malaria in Rwanda, while noting that higher rainfall and the 1987 ENSO were coincident.

The contrast results from the differing effects due to ENSO. Research continues to expand the range of global effects due to ENSO (Glantz et al., 1991), but one major effect is high rainfall in parts of North and South America and Africa, and drought in the southeast Asian and western Pacific region (Ropelewski and Halpert, 1987). While data presented here show an association between lower malaria cases detected and ENSO events, the postulated mechanism of ENSO-related drought leading to reduced vector breeding warrants further investigation.

Despite general recognition of drought during the past three ENSO events (1983, 1987, 1992-93) in Malaysia, the Kelantan monthly rainfall data show only modest difference between ENSO and non-ENSO years (Figures 6 and 7). Ropelewski and Halpert (1987) described a wide region of the western Pacific, including Borneo island, Indonesia, Papua New Guinea, and Australia, that is subject to ENSO-caused
drought. In their map, Peninsular Malaysia is at, or slightly outside, the area of ENSO influence. Thus, the ENSO effect may be attenuated or variable in Kelantan. Trenberth (1991) notes that even though ENSO events are accepted fact, the causes are still only partially defined, and the effects are variable from event to event. Allan (1991) cites a number of studies that relate data on drought and ENSO events and notes that these studies show "close correspondence" but also many "mismatches." For example, from 1844-1976, drought occurred in Java during 28 ENSOs, but there was no drought during eight ENSOs, i.e., 78% of ENSOs were associated with east monsoon droughts in Java (Allan, 1991). It may also be that monthly rainfall data is not appropriately scaled to assess inter-annual events. The ENSO effect may be only a small amplification of the monsoon dry period.

As reliable forecasting of ENSO events improves, government agencies will want to incorporate that information into contingency planning. With better and timely prediction of ENSO events, it may be possible to anticipate changes in malaria occurrence in time to plan more intensive, different, or more selectively targeted malaria interventions. Possible actions might include: 1) temporary reduction of residual house spraying, 2) intensified surveillance and active case detection in areas of low malaria prevalence or unstable malaria incidence, in order to expand the Malaria-Free boundaries, and 3) preparation for a resurgence of malaria transmission following ENSO. It would be prudent to analyze malaria incidence in potential target areas, before and after previous ENSO events.
SEASONALITY AND MALARIA
Variation in Malaria Detected and Correlation of Blood-films Collected with Malaria Detection

The observation that malaria occurrence has annual variation and some seasonal regularity (a peak each year in June, July, or August, and a trough usually seen in April) suggests a cause and effect relationship, but monthly blood-film collections also fluctuate, especially ACD and INV collections, raising the question of whether variation in malaria detection is real or an artifact of sampling. Some malaria staff explain variation by stating that more blood-films equals more cases. This carries two implications: that the actual reservoir of malaria cases is larger than that reflected in the statistics, and that malaria incidence statistics only reflect the work output of the staff. At the same time, some believe that malaria statistics randomly fluctuate unconnected to any objective determinants. For field and supervisory staff, this results from chronic frustration at the failure of intervention tactics to always work according to strategy, i.e., to see a steady, consistent drop in malaria incidence.

From these data, it can be concluded that operational malaria data constitute a sample of actual malaria cases which, though not a strict random sample, is good enough for analysis of trends and variation in malaria incidence.

The largest proportion of total malaria cases in Kelantan State is detected by PCD (43%, Figure 4), representing persons who present to medical facilities with illness. If the intra-annual rise and fall of malaria cases is spurious, these patients must be varying their behavior, or health staff must be varying their criteria of obtaining blood-films or diagnosing malaria. However, there is no evidence for either of these possibilities. In 1991, Kelantan State annual PCD blood-film collection totaled
124,057, ACD blood-films totaled 29,731, and INV blood-films totaled 20,519 (VBDCP Kelantan, 1992).

Correlation coefficients of blood-films collected and malaria positives detected indicate that the number of PCD cases is unassociated with the number of PCD blood-films collected, while the number of PCD cases is highly correlated with PCD Slide Positivity Rate (SPR). This means that the total blood-film collection (the denominator of the SPR) is relatively invariant, that it is the equivalent of a constant, that monthly variation is quite small relative to the variation of the malaria cases. The same is true for ACD. If more blood-films perfectly correlated with more cases, then SPR would be invariant. By contrast, monthly cases detected correlated with monthly SPR, indicating that the denominator, the number of blood-films collected, is relatively invariant, which is the case with PCD and ACD.

INV cases detected do correlate with INV blood-films collected, but monthly INV cases also correlate with INV SPR. Even though increased INV blood-films correlate with more cases detected, the rate of INV detection (SPR) is also higher. This is explained by the correlation between PCD cases and INV blood-film collection: when there is more malaria transmission, more PCD cases are detected, and INV surveys are increased in response to the outbreak. When PCD cases drop, fewer INV blood-films are collected.

The point is that the blood-films collected represent a huge pool of largely negative blood-films. The malaria-positive blood-films detected are a small percentage of total blood-film collection (PCD=7%, ACD=4%, INV=4%). Variations in monthly malaria-positive blood-films are indicative of malaria transmission occurring in the State.
The monthly cases detected separately by PCD, ACD, and INV show correlation, suggesting that the three detection methods each collects blood-films separately, and then the malaria cases detected are correlated, because they reflect actual increase or decrease of transmission. In that ACD blood-film collection and ACD malaria cases were not correlated, it is concluded that Field Canvassers are uninfluenced, by seasonal rise or fall of malaria cases, to change blood-film collection.

**Rainfall**

Both the northeast and southwest monsoons affect Kelantan rainfall. At the coast (Kota Bharu airport, Figure 6), the northeast monsoon causes phenomenally high rainfall in December or November of most years, accompanied by annual flooding, followed by a dry period, then moderate rain until the next flooding. In the interior (Betis, Figure 7) where malaria transmission actually occurs, the seasonality is less easily characterized, but high rainfall usually occurs in one month during October-December, due to the northeast monsoon, and in 1-3 months during the middle of the year, due to the southwest monsoon.

**Association of Rainfall and Malaria Incidence**

The association between rainfall and malaria (Figure 8) is interesting and complex. When monthly composite rainfall (three-month moving average of mean rainfall from six interior rain stations) rises above 200 mm per month, there is a marked drop in next month's malaria incidence. When rainfall drops back to lower levels, incidence rises. Rainfall between approximately 100-200 mm per month
appears to be conducive to malaria transmission. During periods of drought, with rain less than 100 mm per month, next month's incidence drops again.

The association between malaria transmission and rainfall is never explicitly mentioned in the VBDCP annual reports. The flushing effect of heavy rainfall on An. maculatus breeding sites is mentioned in the literature and is common knowledge to entomology technicians in the field, and likewise, the drying up of breeding sites during drought is known, but these two associations have not been linked, nor has anyone defined quantitative parameters.

Rahman et al. (1993) collected data for one year, January-December 1990, in a village of Perak state (west of Kelantan). They described a positive correlation between monthly malaria and An. maculatus density and a negative correlation between vector density and rainfall (referring to high vector density and high malaria cases during low rainfall, and vice versa). They do not mention it, but their data can also be interpreted as a positive association between low rainfall and decreasing vector density and malaria cases. In their study area, rainfall was < 100 mm per month for January-May, vector density peaked in February, malaria cases peaked in March, then both vector density and malaria cases continued to sink and stay low from June-December. During September-November, rainfall was > 200 mm per month.

Although rainfall itself is not amenable to intervention, rainfall can be monitored to heighten awareness of changing risk of malaria transmission. Since entomological surveillance is so often unproductive in the context of chronically low An. maculatus density, changes in rainfall could be a useful substitute indicator of changes in malaria risk. With forewarning of increased malaria risk, malaria staff could increase their diligent efforts, prepare for increasing number of patients, and
initiate public information campaigns (e.g., radio and television announcements) that could promote personal protection (e.g., bednet use) during the higher transmission seasons. In addition, rainfall could be used as a rational explanation in annual reporting.

Durian and rubber seasons may be acting as co-determinants during part of the year, but this could not be confirmed. Although the peak of malaria incidence coincides with the suggested durian and rubber seasons, increase of malaria incidence starts before the durian season, and drops before the end of rubber season. In other words, the association between either season and increased malaria incidence is imperfect: the hypothesized effect (increased malaria transmission) begins before the beginning of one cause (durian season) and ends before the finish of the second cause (rubber season).

AGE- AND SEX-SPECIFIC RISK GROUPS BY BLOOD-FILM COLLECTION METHOD

Age-specific malaria case totals are difficult to assess without knowing the age structure of the population at-risk. Stratified sex-specific or age-specific case data are routinely tabulated by VBDCP, but cross-tabulation is not done. Stratified tabulation of blood-films is not available (due to the manpower and computer constraints). Age- and sex-specific census data for individual malaria sectors are also unavailable, although total population estimates are available. In this study, cross-tabulated age- and sex-specific malaria incidence data for Gua Musang District for 1991 were presented.

Although age- and sex-specific census data were unavailable for the study area, it was possible to show that the blood-filmed population that was sampled by the three
collection methods resembled the district census population in age structure (Figure 11) and male:female ratio. Because the district census population and the blood-film collection had similar age structures, the age-specific incidence of malaria (malaria cases/1000 population) also resembled the age-specific malaria cases/1000 blood-films. On this basis, the blood-film collection was used as a substitute denominator for the unavailable age- and sex-stratified census data.

Age distribution of the blood-film collection was bimodal with one peak in children 5-9 years old (consistent with both district and State census data), while the second peak in persons 20-24 years old matched the district census data, but contrasted with the State census data (Figure 11). Age- and sex-specific stratification showed that the peak of the blood-film collection in children occurred in both sexes, but the peak in young adults was due to more males (Figures 14, 15, and 16). This was consistent with the fact that Gua Musang attracts many young, single males to work in timber and plantation schemes.

Malaria cases/1000 blood-films showed peaks in young children 1-4 years old, young adults 15-29 years old, and in persons 50-54 years old (Figure 13). Age- and sex-specific stratification showed that malaria was higher in males in virtually all age groups (Figure 17). Adult males have greater occupational exposure to malaria, but apparently males at all ages have greater risk of malaria infection.

The bimodal distribution and heavy skewing towards males differs from previous descriptions of epidemiologic parameters of parasitemia in Malaysia. As mentioned in Chapter 2, previous studies have described two types of age-specific parasitemia in Malaysia: in Orang Asli, parasitemia rises quickly in age group 0-4 years old, plateaus by age nine, and then decreases to zero in adults; in Malay
populations, parasitemia simply increases with age. The Gua Musang population was clearly different, probably reflecting the heterogeneous mix of local Malay villagers with economic migrants, both Malaysian and foreign.

PCD was more effective than ACD or INV in detecting malaria cases overall, in both males (Figure 18) and females (Figure 19), but particularly in children, teenagers and young adults. However, highest incidence in males 35 years and older was detected by INV.

*P. falciparum* gametocytemia was generally low in males (<30/1000) and even lower in females (<22/1000); however, ACD and INV were generally better than PCD at detecting gametocyte carriers (Figure 20, Figure 21). The age- and sex-specific groups that emerged as risk groups for gametocytemia were: young children (1-9 years) as detected by ACD; teenage and young adult males (15-29 years) as detected by ACD and INV; older adult males (35-54 years old) as detected by INV.

PCD is the primary method of detecting malaria cases, but ACD and INV were shown to have an important role for detection of gametocyte-carriers that contribute to continued transmission of malaria. ACD and INV were also useful for detection of malaria in age- and sex-specific risk groups. ACD and INV blood-film collections have high costs associated with field staff salary and travel allowances, but these methods can be important and cost-effective in detecting hidden reservoirs of transmission risk in gametocytemic persons and persons with asymptomatic infection. Specific targeting of age- and sex-specific risk groups could be emphasized, but not at the exclusion of other groups which still suffer malaria infection.

MCPs collect, log, and then store vast amounts of primary data on malaria. Analysis of these data have significance for improving operations only in terms of the
specific MCP, but operational research should strive to use this valuable resource to its fullest extent.

CASE-CONTROL SUBSTUDY IN KAMPUNG JEREK

The case-control substudy examined environmental and personal determinants of malaria infection within the geographical locality of a large village (kampung) in Kelantan, Malaysia. Residents of the village who had been blood-filmed during periodic house-to-house canvassing were included. Malaria-positive individuals were matched with malaria-negative neighbors, based on age and same date of blood sampling. Determinants examined included housing (type, construction, size, residual insecticiding), vector breeding sites, bednet use, other personal protection measures, and knowledge, attitudes, and practices related to malaria transmission.

The small sample size (22 case-control pairs) may have denied detection of risk factors. Under the original study plan, the candidate had hoped to obtain cases and non-cases identified through PCD at hospital and clinics in the vicinity. A patient would then become a case or non-case, based on positive or negative diagnosis of a blood-film. The intention was to match on same village, same week of blood-film examination, and similar age-group. Two problems arose: 1) small number of cases (and smaller number of matching non-cases) due to extraordinary seasonal factor (drought and decreasing malaria transmission) made it difficult to acquire sufficient cases and impossible to match on same village, same week, and same age group; and 2) lack of full and correct address in the register book made it very difficult to trace the case and non-case in the villages.
The study plan was modified to use ACD and INV/MBS blood-film results for the whole of 1991. This promised a larger pool of positive blood-films. Furthermore, the large number of blood-films collected in the span of a few days made it possible to carry out age-matching. With the original survey forms of 1991 still available, even when a house number was omitted from the form, it was still possible to follow the order of blood-film collection and arrive in the vicinity of the case or non-case house and trace the person.

The study concentrated on Kampung Jerek, because this village had a high number of cases in the past, and it was known from previous investigation that transmission occurred in the village. Furthermore, VBDCP staff were familiar with the village facilitating tracing of individuals.

Because this study interviewed people as much as one year after their blood-filming, recall error was a problem, especially when asking people where they may have travelled prior to the blood-film, whether they used a bednet, took prophylactic drug, etc. We were asking people to recollect their behavior, movements, and symptoms from as long as one year previous. Furthermore, we were asking the non-cases to recollect a time when they did not have malaria. Recall bias was suspected of reducing variation between case and non-case (e.g. both would answer, yes, I only slept in the village; yes, I used a bednet). It was difficult to verify any answers given by the respondents--they had to be accepted at face-value.

Case-control methodology can be useful for examining risk factors of malaria infection, if it can be used in a locality of relatively abundant cases and shortly after the blood-film collection and diagnosis to ensure accurate interviews. Our experience with interviewing patients many months after their blood-filming (whether positive or
negative) showed that recall of important risk factors was difficult to establish with certainty. At a time of low incidence in Kelantan, it was difficult to find enough cases and non-cases to ensure an adequate sample size.

CONCLUSIONS

1. Inter-annual decrease of malaria cases detected in Peninsular Malaysia, Kelantan, and Sabah is associated with ENSO events. The postulated mechanism, of ENSO-related drought leading to reduced vector breeding, warrants further investigation to bring to bear entomological data.

   Reliable forecasting of ENSO events raises policy implications with regard to possible modifications of antimalaria actions. A general prediction for decreased malaria incidence might suggest reallocation of intervention resources, e.g., to intensify surveillance and case detection in areas of low or unstable prevalence in order to expand the Malaria-Free zones, to temporarily reduce residual house spraying, to prepare for a post-ENSO increase of transmission.

2. Malaria incidence in Kelantan State shows an association with rainfall by a composite model of either: a) decreasing malaria incidence when rainfall is high or low (empirically observed to be greater than 200 mm per month or less than 100 mm per month), or b) increasing malaria incidence when intermediate rainfall is conducive to transmission. These observations are consistent with the known flushing effect of vector breeding sites by flooding and the drying of breeding sites by drought.

   Although rainfall itself is not amenable to intervention, the cognizance of heightened risk of malaria transmission (due to changes in rainfall) could be used by
malaria staff to increase their diligent efforts and to promote malaria awareness and personal protection (e.g., bednet use) among the public.

3. Malaria incidence in Gua Musang District during 1991, as detected by all blood-film collection methods, was bimodal on young children and young adult males, probably reflecting the dual makeup of this district: a) rural villages where malaria infection most affects the youngest age groups with less immunity, or b) plantations and timber camps that attract tropical labor aggregations of single, young adult males.

4. PCD blood-film collection was the most efficient method of detecting malaria (of all species) in Gua Musang District during 1991, but ACD and INV were important for detecting malaria in certain age- and sex-specific categories: males 35 years and older by INV, and males 15-29 years old by ACD and INV. Furthermore, ACD and INV were important in detecting gametocyte-carriers in specific groups: young children (1-9 years, male and female) as detected by ACD; teenage and young adult males (15-29 years) as detected by ACD and INV; and older adult males (35-54 years old) as detected by INV.

Although ACD and INV blood-film collection are believed to have higher costs associated with field staff salary and travel allowances, these methods could be important and cost-effective in detecting hidden reservoirs of transmission risk in gametocytemic patients and persons with asymptomatic infection.
Figure 1. Annual malaria incidence of Malaysia, Peninsular Malaysia, Sabah, Sarawak, and Kelantan, 1980-92.
Sources: VBCP Kelantan; VBCP Malaysia, 1993; Mak et al., 1992.
Figure 2. Peninsular Malaysia.
Figure 3. Kelantan State malaria sectors, 1991.
Figure 4. Malaria cases detected, by collection source, and by district, Kelantan State, 1991. Source: VBDCP Kelantan.
Figure 5. Annual malaria cases in relation to El Niño Southern Oscillation (ENSO) events in Peninsular Malaysia, Sabah State, and Kelantan State, 1961-92.

Sources: VBDCP Kelantan; Mak et al., 1992.
Figure 6. Monthly rainfall, Kota Bharu airport station, Kelantan, and El Niño Southern Oscillation (ENSO) events, 1970-91.
Sources: Department of Meteorology Malaysia, 1970-91; Philander, 1983.
Figure 7. Monthly rainfall, Orang Asli Betis station, Kelantan, and El Niño Southern Oscillation (ENSO) events, 1974-91.
Sources: Department of Meteorology Malaysia, 1970-91; Philander, 1983.
Figure 8. Monthly malaria incidence (PCD+ACD cases) and monthly mean rainfall (six stations [see text]), Kelantan State, 1980-91.
Sources: VBDCP Kelantan; Department of Meteorology Malaysia, 1970-91.
Figure 9. Three-month moving averages of malaria incidence (PCD+ACD cases) and mean rainfall (6 interior stations [see text]), Kelantan State, 1980-91.
Sources: VBDCP Kelantan; Department of Meteorology Malaysia, 1970-91.
Figure 10. Monthly rubber price and monthly New Rubber production, Peninsular Malaysia, 1985-91.
Figure 12. Age-specific incidence of malaria and age-specific blood-film collection rate, Gua Musang District, 1991.
Figure 13. Age-specific incidence of malaria cases per 1000 population and of malaria cases per 1000 blood-films, Gua Musang District, 1991.
Figure 14. Percent distribution by age and sex of the PCD blood-film sample population (n=2123), Gua Musang District, 1991.
Source: VBDCP Kelantan.
Figure 15. Percent distribution by age and sex of the ACD blood-film sample population (n=6422), Gua Musang District, 1991.
Source: VBDCP Kelantan.
Figure 16. Percent distribution by age and sex of the INV blood-film sample population (n=3221), Gua Musang District, 1991.
Source: VBCDP Kelantan.
Figure 17. Age- and sex-specific incidence of falciparum (Pf) or vivax (Pv) parasitemia, all sources (ACD/PCD/INV), blood-film sample population, Gua Musang District, 1991. Source: VBDCP Kelantan.
Figure 18. Age-specific male incidence of falciparum and vivax malaria in the blood-film sample population, by blood-film collection method, Gua Musang District, 1991.
Source: VBDCP Kelantan.
Figure 19. Age-specific female incidence of falciparum and vivax malaria in the blood-film sample population, by blood-film collection method, Gua Musang District, 1991. Source: VBDPC Kelantan.
Figure 20. Age-specific male incidence of falciparum gametocytemia, in blood-film sample population, as detected by ACD vs INV vs PCD, Gua Musang District, 1991. Source: VBDCP Kelantan.
Figure 21. Age-specific female incidence of falciparum gametocytemia, in blood-film sample population, as detected by ACD vs INV vs PCD, Gua Musang District, 1991.
Source: VBDCP Kelantan.
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<tr>
<th>No.</th>
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<tr>
<td>1. Date of Interview:</td>
<td>/ / 92</td>
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<tr>
<td>2. Place of Inquiry:</td>
<td></td>
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<tr>
<td>3. Date of Slide:</td>
<td>/ /</td>
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<td>4. Result: Pf • Pv • Pm • Pfg • NEG</td>
<td></td>
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<tr>
<td>5. Density:</td>
<td></td>
</tr>
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<td>6. Source of Slide:</td>
<td>PCD • ACD • INV</td>
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<td>7. Name:</td>
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<tr>
<td>8. Age:</td>
<td></td>
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<td>9. Sex:</td>
<td>M • F</td>
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<td>10. Normal Address:</td>
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<td>11. Nationality:</td>
<td>Malaysia • Indonesia • Thailand • Burma • India • Other:</td>
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<td>12. Ancestry:</td>
<td>Malay • Thai • Chinese • Indian • Aborigine • Other:</td>
</tr>
<tr>
<td>13. Occupation:</td>
<td>Young child • Student • Farmer • Housewife • Commerce • Timber • Rubber-tapper • Estate-laborer • Coconut-laborer • Other:</td>
</tr>
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<td>14. Geography of area:</td>
<td>Mountainous • Hilly • Flatland • Rivershore • Seashore • Other:</td>
</tr>
<tr>
<td>15. Type of area:</td>
<td>City • Village • Estate • Dormitory • Fruitgrove • Forest • Other:</td>
</tr>
<tr>
<td>16. Wall Material:</td>
<td>Wood • Stone • Bamboo • Thatch • Zinc • Mixed • Other:</td>
</tr>
<tr>
<td>17. Form of Walls:</td>
<td>Complete • Partial walls • Less than four walls • Openwork • None</td>
</tr>
<tr>
<td>18. DDT spraying of House:</td>
<td>Complete • Partial • None • Not in a spray zone</td>
</tr>
<tr>
<td>19. Date of last spraying:</td>
<td><em><strong>/</strong></em>/___</td>
</tr>
<tr>
<td>20. Is there a mosquito breeding site within 250 meter?</td>
<td>Yes • No</td>
</tr>
<tr>
<td>21. How many people usually sleep in the house?</td>
<td></td>
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<tr>
<td>22. How many sleeping rooms in the house?</td>
<td></td>
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<tr>
<td>MALARIA FEVER HISTORY</td>
<td></td>
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<tr>
<td>23. Date of Fever Onset (IN CASE):</td>
<td>Where sleeping during 14 days before date of fever? (Cite all places visited.)</td>
</tr>
<tr>
<td>24. Ever have malaria before?</td>
<td>Yes • No</td>
</tr>
<tr>
<td>When?</td>
<td></td>
</tr>
<tr>
<td>Where?</td>
<td></td>
</tr>
<tr>
<td>Medication taken?</td>
<td></td>
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<tr>
<td>25. How many times?</td>
<td></td>
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<tr>
<td>26. Medication from where:</td>
<td>clinic/hospital • GP • FC/RKPBV • shop • traditional • self</td>
</tr>
</tbody>
</table>
27. According to your understanding, how is malaria spread to people?
   - Don't know
   - By stagnant water
   - By food
   - Mosquitoes
   - Other insects
   - Other:

28. What are the signs of malaria sickness?
   - Don't know
   - High fever
   - Headache
   - Shaking/chills
   - Vomiting
   - Other:

29. How is malaria prevented or controlled?
   - Don't know
   - Preventive medicine
   - DDT spraying
   - Bednet use
   - Mosquito coils
   - Other:

PROPHYLAXIS (Case and control before fever date/before blood collection)

30. Do you take medicine against malaria, even when healthy?
   - Never
   - Only with fever
   - Occasionally
   - Always

31. Do you usually use/burn mosquito coils?
   - Never
   - Occasionally
   - Always

BEDNET (Case and control before fever date/before blood collection)

32. Do you own a bednet?
   - Yes
   - No

33. Did you sleep inside a bednet?
   - Last night
   - Last week

34. If did not use bednet, then why?
   - Too hot
   - No mosquitoes
   - Don't know/no answer

35. Before the date of fever/before blood collection, did you usually sleep in bednet?
   - Always
   - If mosquitoes bother
   - Occasionally
   - Never

36. What time do you go to bed?
   - PM

37. What time do you get up?
   - AM

38. NIGHTIME MOVEMENT/ACTIVITIES (during two weeks before date of fever/blood collection)
   - Never go out of house
   - Occasionally go out of house
   - Forest work
   - Fishing
   - Hunting
   - Visit friends
   - Watch TV
   - Go to shop/market
   - Other:

39. INDICATORS OF SOCIOECONOMIC STATUS
   - Electricity
   - Piped water
   - Radio
   - TV
   - Wardrobe
   - Sofa set
   - Motorcycle
   - Auto
<table>
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<th>Bil.</th>
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<td>Jantina: * L * P *</td>
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</table>
| 13.  | Pekerjaan: * Kanak-kanak * Pelajar * Petani * Surirumah * Perniaga * Pembalek *
|      | * Penoroh * Buruh-estet * Buruh-kelapa sawit * Lain: |
| 14.  | Kawasan Geografi: * Gunung * Bukit * Tanah rata * Tepi sungai * Tepi laut * Lain *
| 15.  | Keadaan Rupa Bumi: * Bandar * Kampung * Estet * Kongsi * Dusun * Hutan * Lain *
| 16.  | Bahan Dinding: * Kayu * Batu * Buluh * Atap * Zin * Campor-campor * Lain *
| 17.  | Bentuk Dinding: * Lengkap * Separoh lengkap * Kurang empat dinding * Berpagar * Tiada *
| 18.  | Semburan DDT di Rumah: * Semua * Separoh * Tidak ada * Kawasan tidak menyembark *
| 19.  | Tarikh semburan terakhir: _/__/__ |
| 20.  | Adakah tempat nyamuk membiak dalam jarak 250 meter? * Ya * Tidak *
| 21.  | Berapa orang biasa bermalam di rumah? |
| 22.  | Berapa bilik-tidur di rumah? |
| 23.  | Tarikh Deman Bermula (kes): |
|      | Dimana-kah bermalam selama 14 hari sebelum tarikh demam? (Sebut semua tempat berjalan.) |
| 24.  | Sudah pernah deman malaria? * Ya * Tidak *
<p>|      | Bilah? |
|      | Dimanakah tempat? |
|      | Makan ubat? |
| 25.  | Berapa kali? |
| 26.  | Ubat dari mana: * klinik/hospital * GP * FC/RKPBV * kedai * tradisi * sendiri * |</p>
<table>
<thead>
<tr>
<th>PENGGETAHUAN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>27. Pada pengetahuan anda, bagaimana malaria berjangkit ke orang?</td>
<td>Tidak tahu * Bawaan air takongan * Bawaan makan *</td>
</tr>
<tr>
<td></td>
<td>Bawaan Nyamuk * Bawaan serangga lain * Lain:</td>
</tr>
<tr>
<td>28. Apakah tanda-tanda penyakit malaria?</td>
<td>Tidak tahu * Demam panas * Sakit kepala * Ketar * Muntah * Lain:</td>
</tr>
<tr>
<td>29. Bagaimana malaria di-cegahkan atau di-hapuskan?</td>
<td>Tidak tahu * Makan ubat pencegahan * Semburan DDT * Guna kelambu * Ubat nyamuk *</td>
</tr>
<tr>
<td></td>
<td>Lain:</td>
</tr>
</tbody>
</table>

PROPHYLAXIS (Pesakit/rujuk sebelum tarikh demam/sebelum peperiksa dara)

30. Anda biasa makan ubat mencegah malaria, walaupun sihat?        | Tidak-pernah * Kalau-demam-sahaja * Kadang-kadang * Selalu * |
| 31. Anda biasa pakai/bakar ubat nyamuk?                          | Tidak-pernah * Kadang-kadang * Selalu * |

KELAMBU (Pesakit/rujuk sebelum tarikh demam/sebelum peperiksa dara)

32. Anda punya kelambu? * Ya * Tidak *  |
33. Anda tidur dalam kelambu? * Kalau-nyamuk * Minggu-nyamuk *  |
34. Kalau tidak pakai kelambu, kenapa? * Panas * Tiada-nyamuk * Tidak-tahu/tidak-jawapan *  |
35. Waktu sebelum tarikh demam/sebelum peperiksa dara, anda biasa tidur dalam kelambu? | Sinxlabel * Kalau-nyamuk-ganggu * Kadang-kadang * Tidak-pernah * |


38. PERJALANAN PESAKIT DI WAKTU MALAM (semasa dua minggu sebelum tarikh demam/periksa dara) |
| Tak Pernah Keluar Rumah * Kadang-kadang keluar rumah * Kerja hutan * Pancing * |
| Berburu * Melawat kawan * Tengok TV * Keluar ke kedai/pasar * Lain: |

39. PERALATAN/KEHADUHAN |
| Letrik * Bakalan air * Radio * TV * Almari * Kerusi set * Motosikal * Kereta * |
APPENDIX C

CASE-CONTROL DESCRIPTION
Sex
Age
Person Interviewed
Blood-film result
Density
Nationality
Ancestry
Occupation

HOUSE
Topography: Flat/Hilly
Type of Area: Village/Open country
Wall Material: Solid wood/Mixed material
Form of Walls: Closed construction/Open spacing

DDT House Spraying: Present/Absent
When was House sprayed relative to onset of infection: Yes/No
Breeding Site within 250 m.: Yes/No
No. of people sleeping in house:
No. of sleeping rooms:
Did transmission take place in village? Yes/No/Maybe
Previous Malaria?: Yes/No
Multiple previous malaria?: Yes/No
Recent malaria (less than 1 year): Yes/No
Recent Malaria? <y> (kurang 1 tahun)
Previous malaria--where?
Got medication from where

KNOWLEDGE
How is malaria transmitted from person to person?
Don't know
by stagnant/foul water
by food
by mosquitoes
by other insects
by other means

Symptoms of Malaria
Don't know
Fever
Headache
Shivering/Chills
Vomiting
other

Prevention of Malaria
Don't know
Take medicine
House spraying
Bednet
Mosquito coils
Clean/clear the compound of trash
Clean/sanitary water
Clean/sanitary food
other

PROPHYLAXIS
Take protective medicine: never/fever only/occasionally/always
Use mosquito coils: never/occasionally/always

BEDNET
Own a bednet?: Yes/No
Used it last night?: Yes/No
Used it last week?: Yes/No
If not using, then why?
Was bednet used before the onset of the case?: Yes/No
What time retiring?
What time arising?

NIGHT TIME ACTIVITIES
Never go out: Yes/No
Occasionally go out: Yes/No
Forest work: Yes/No
Fishing: Yes/No
Hunting: Yes/No
Visit friends: Yes/No
Watch TV: Yes/No
Go shop/market: Yes/No
Read Koran: Yes/No
Other

INDICATORS OF SOCIOECONOMIC STATUS
Electricity: Yes/No
Piped water: Yes/No
Radio: Yes/No
TV: Yes/No
Wardrobe/Cupboard: Yes/No
Sofa set: Yes/No
Motorcycle: Yes/No
Auto: Yes/No
REFERENCES


